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COAGULATION DEFECTS INDUCED BY LONG-TERM ANTICOAGULANT THERAPY* †

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Since the introduction of anticoagulant therapy, the prothrombin time as originally determined by Quick, has been used as a means of controlling dosage. Hemorrhage is the major complication of anticoagulant therapy. In one type of hemorrhage, the prothrombin time is greatly prolonged and the bleeding can be explained on the basis of prolonged coagulation reactions. In the second type, the prothrombin time is in the therapeutic range and the mechanism of bleeding is not clear. In many instances the bleeding is minor in nature, *e.g.*, hematuria, bruising or petechiae. Recent studies indicate that many of the episodes of bleeding in the second type may be related to coagulation factors which are not measured by the prothrombin time (1–4) but may be measured by the thromboplastin generation test.

The purpose of the present investigation is to characterize the coagulation defects that may occur during long-term anticoagulant therapy and to correlate these findings with the past history of hemorrhage. A comparison is also made with the defects found in patients with severe liver disease.

MATERIALS AND METHODS

Selection of patients. Of the 300 patients under investigation, 40 had been receiving anticoagulant therapy continuously for a minimum period of six months; these 40 were examined weekly in the Out-Patient Clinic of Jackson Memorial Hospital. The other 260 were private patients who were seen at varying intervals. Most of the patients had arteriosclerotic heart disease and a past history of myocardial infarction; many had had more than one infarction. The severity of the cardiac disease and the nature of its management were not taken into consideration in evaluating the data.

Control specimens of blood were obtained from normal persons. Sera from patients

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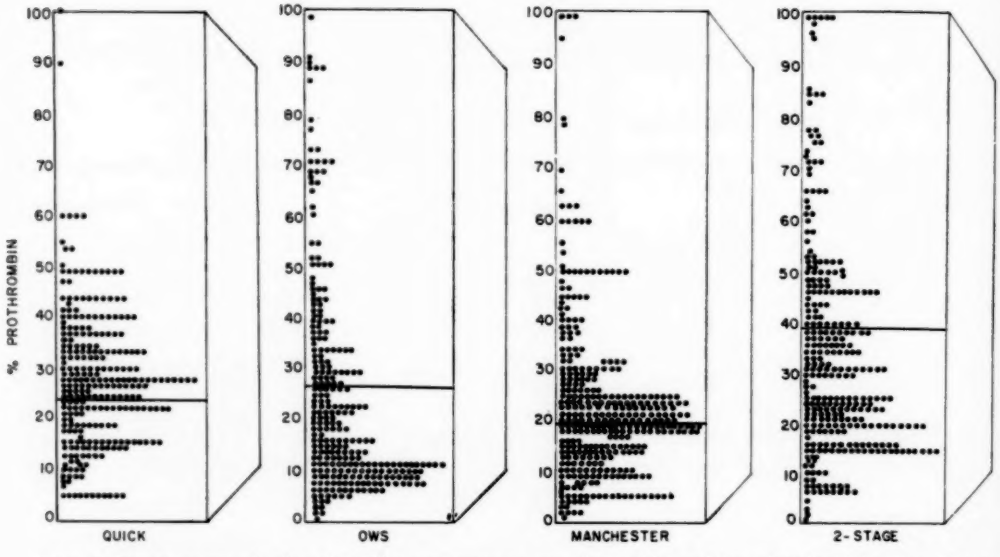

FIG. 1. Scatter graph showing the percentage prothrombin values obtained by the Quick, the Owren-Ware-Stragnell, the Manchester one-stage, and the Ware and Seegers two-stage methods in a series of 350 determinations on the blood of patients receiving long-term anticoagulant therapy. The horizontal lines indicate the mean value for each method.

with known deficiencies of plasma thromboplastin component (PTC)[1], Stuart-Prower factor[1], plasma thromboplastin antecedent (PTA)[2] and Hageman factor[3] were used as indicated under Results. Blood from patients with severe liver disease (Laennec's cirrhosis) was also tested as described subsequently.

Coagulation studies. Venous blood was collected from non-fasting patients. Blood that had been allowed to clot in glass test tubes at 25°C. was used to determine the clotting time; aliquots of the serum were incubated at 37°C. for one hour and for four hours after clotting for the prothrombin consumption and the thromboplastin generation tests respectively. Plasma was obtained from whole blood to which 0.1 *M* potassium oxalate solution had been added. Plasma and serum were separated by centrifugation at 3,000 r.p.m. (25°C.) for fifteen minutes. Platelet-rich plasma was obtained from whole blood to which 3.8 per cent sodium citrate solution had been added in siliconized test tubes. The erythrocytes were allowed to settle at 25°C. for fifteen minutes and the supernatant plasma was removed for use in the thrombin generation test.

Brain phospholipid (25 mg./per ml.) was prepared as described by Bell and Alton (5) and stored at −20°C. until used. In the thromboplastin generation test (6), unless otherwise indicated, brain phospholipid replaced platelet suspensions according to the modification described by Bell and Alton. Quick's one-stage prothrombin time (7) was determined using human brain thromboplastin with 0.025 *M* calcium chloride. The Owren-Ware-Stragnell prothrombin time was determined as described by Ware and Stragnell (8). The Manchester prothrombin test was performed as described by Manchester and Rabkin (9). The Ware and Seegers two-stage prothrombin determination (10) was modified by the use

[1] Courtesy of Dr. John Graham, Department of Pathology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

[2] Courtesy of Dr. Irving Woldow, Department of Hematology, Albert Einstein Medical Center, Philadelphia, Pennsylvania.

[3] Courtesy of Dr. Oscar Ratnoff, Department of Medicine, Western Reserve School of Medicine, Cleveland, Ohio.

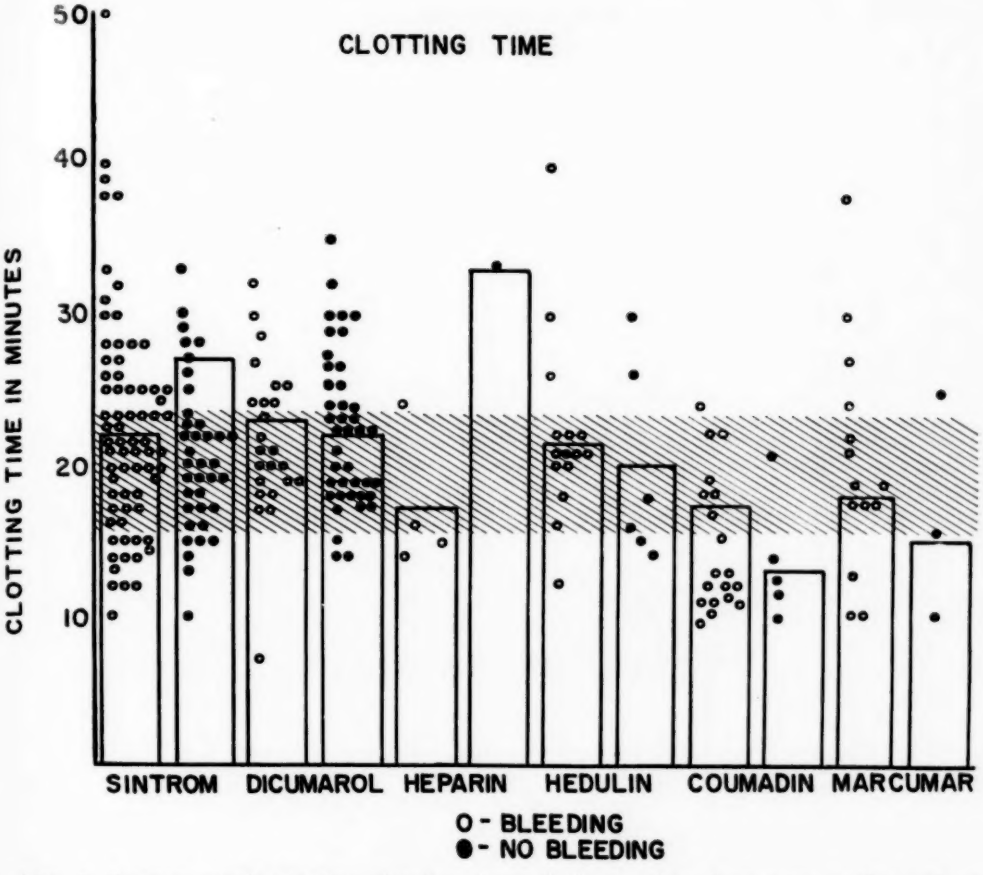

FIG. 2. Scatter graph showing clotting times during various long-term anticoagulant regimens. The circles represent data on patients with a past history of bleeding. The black dots represent data on patients without any known bleeding episodes. The shaded areas indicate the normal range for the various determinations. The height of each bar indicates the mean value for that determination.

of bovine serum and a preparation[4] of Fraction I which had been purified by adsorption with barium sulfate and subsequent precipitation with 25 per cent ammonium sulfate. Fibrinogen (fibrin) determinations were carried out by a method previously described by Boyles *et al.* (11). Factor V (Ac-globulin) was estimated by the one-stage method of Stefanini (12). The prothrombin consumption test of Quick and Favre-Gilly (13) was modified by employing bovine Fraction I to replace deprothrombinized plasma. Thrombin generation was determined by the method of MacFarlane and Biggs (14). Recalcification time was carried out by Quick's method (15). Clotting time was determined by the Lee and White technique (16). Factor VII (proconvertin) was estimated by the one-stage method of Owren and Ans (17). Platelet adhesiveness was assayed by the technique of Moolten and Vroman (18). Electrophoresis was carried out in a Spinco-Durrum type cell at 10°C. The serum (6 gamma) was applied to an equilibrated electrophoresis apparatus using Veronal buffer,[5] pH 8.6, ionic strength 0.050. A potential of 150 volts with constant current at 5 milliamperes was maintained for twenty hours. Bromophenol blue was used

[4] The Armour Company, Chicago, Illinois.

[5] Barbital buffer.

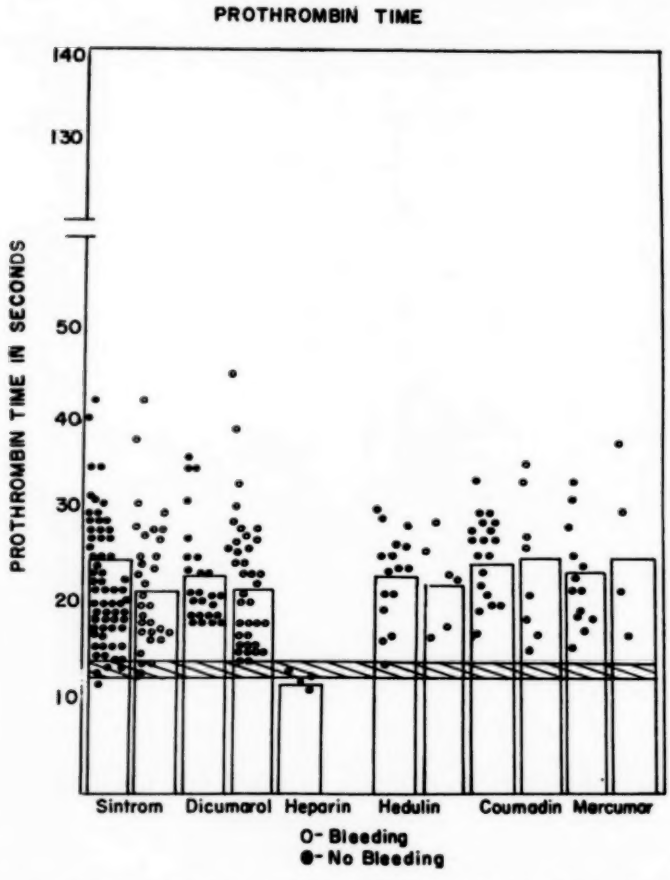

FIG. 3. Scatter graph showing prothrombin times during long-term treatment with various anticoagulants. For key to symbols, see legend to Figure 2.

for protein staining. Quantitation of the protein fractions was obtained by a Spinco analytic photoelectric scanner. Bromsulphalein retention at forty-five minutes after injection of the dye (5 mg./Kg.) was determined by a colorimetric method.

RESULTS

The 300 patients studied had been treated with anticoagulants for at least six months. Each blood specimen demonstrated multiple-factor deficiencies. Subsequent to the performance of the blood studies the patients' charts were analyzed for any "recognized" past history of hemorrhage.

Prothrombin time. Prothrombin times were determined simultaneously by the one-stage methods of Quick, of Manchester and Rabkin, and of Owren, Ware and Stragnell, and by the two-stage procedure of Ware and Seegers. Approximately 350 determinations were made with each method. Figure 1 illustrates the percentage of prothrombin as determined by these techniques. With the two-stage method, a consistently higher percentage was obtained than with the other methods, but it closely approximated the results obtained with the Owren-Ware-Stragnell one-stage method.

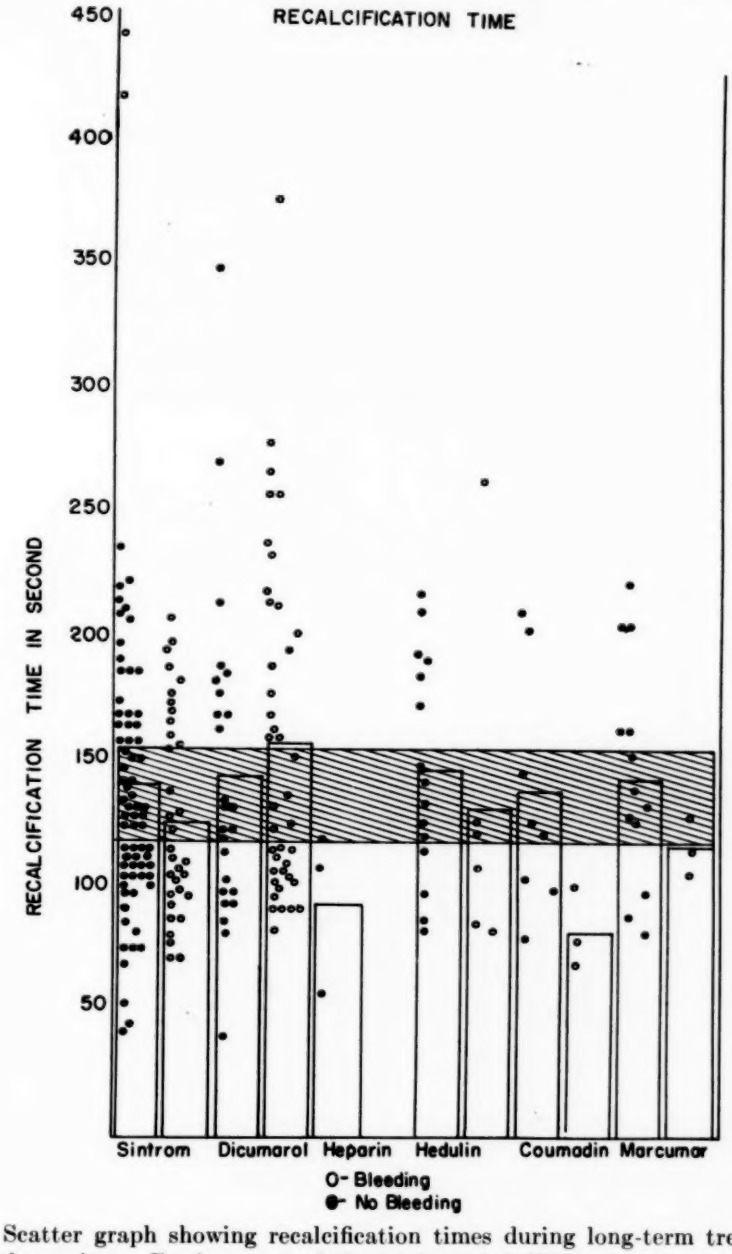

FIG. 4. Scatter graph showing recalcification times during long-term treatment with various anticoagulants. For key to symbols, see legend to Figure 2.

Coagulation defects. In addition to the known effects of long-term anticoagulant therapy on prothrombin conversion factors, all the oral anticoagulants studied induced abnormal generation of thromboplastin (Figs. 2–8). No significant difference was noted between them, in this respect, with the exception of heparin. Heparin primarily caused prolongation of the clotting time as well as abnormal thromboplastin generation. In addition, no discernible difference was noted in the coagulation defects produced, whether or not the patients had histories of

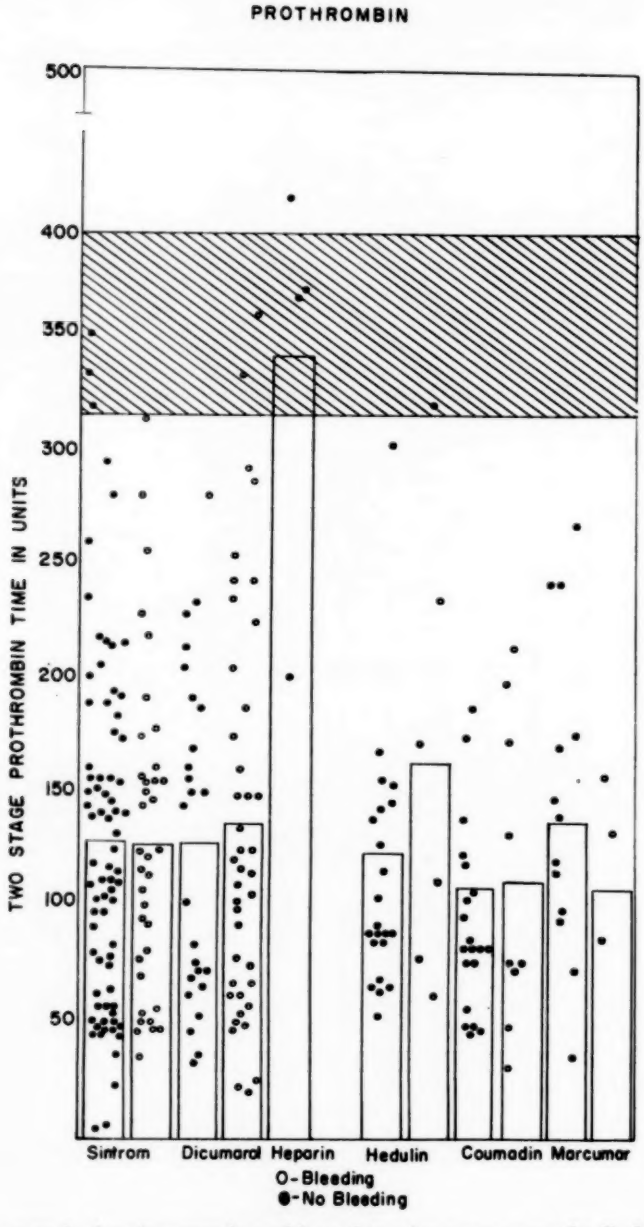

FIG. 5. Scatter graph showing prothrombin values (two-stage method) during long-term treatment with various anticoagulants. For key to symbols, see legend to Figure 2.

bleeding. Factor V (accelerator globulin), fibrinogen, platelets and the platelet adhesive index were within the normal range in all the patients studied. On the other hand, thrombin generation was consistently abnormal in all the patients.

Defects in thromboplastin generation. Both long-term anticoagulant therapy and severe liver disease produced defective generation of thromboplastin in addition to the known effects on prothrombin conversion factors.

Identification of the serum factors accounting for the abnormal thromboplastin

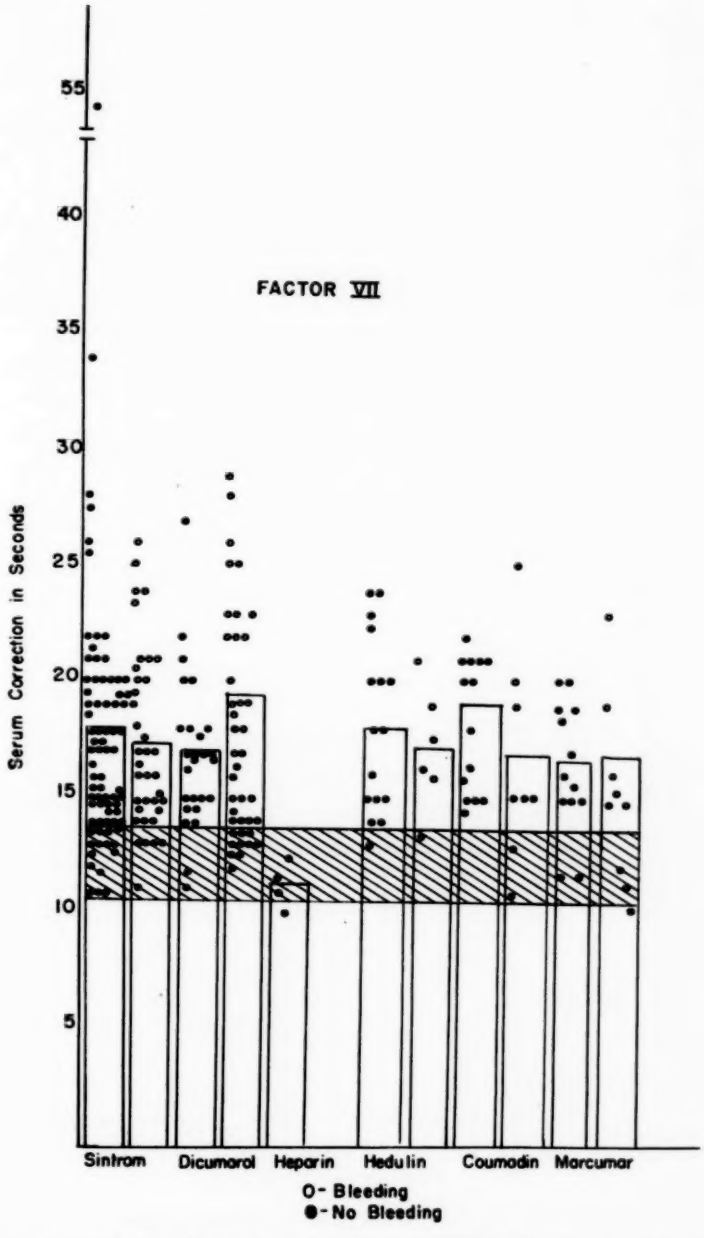

FIG. 6. Scatter graph showing values for Factor VII during long-term treatment with various anticoagulants. For key to symbols, see legend to Figure 2.

generation was made by cross-matching experiments. This was accomplished by mixing sera from patients receiving anticoagulants with sera from patients known to be congenitally deficient in a specific serum thromboplastic factor. Results of these studies demonstrated that the defects were due to a relative deficiency of PTC and Stuart and Hageman factors. Patients with severe liver disease had similar coagulation defects and their serum did not correct the

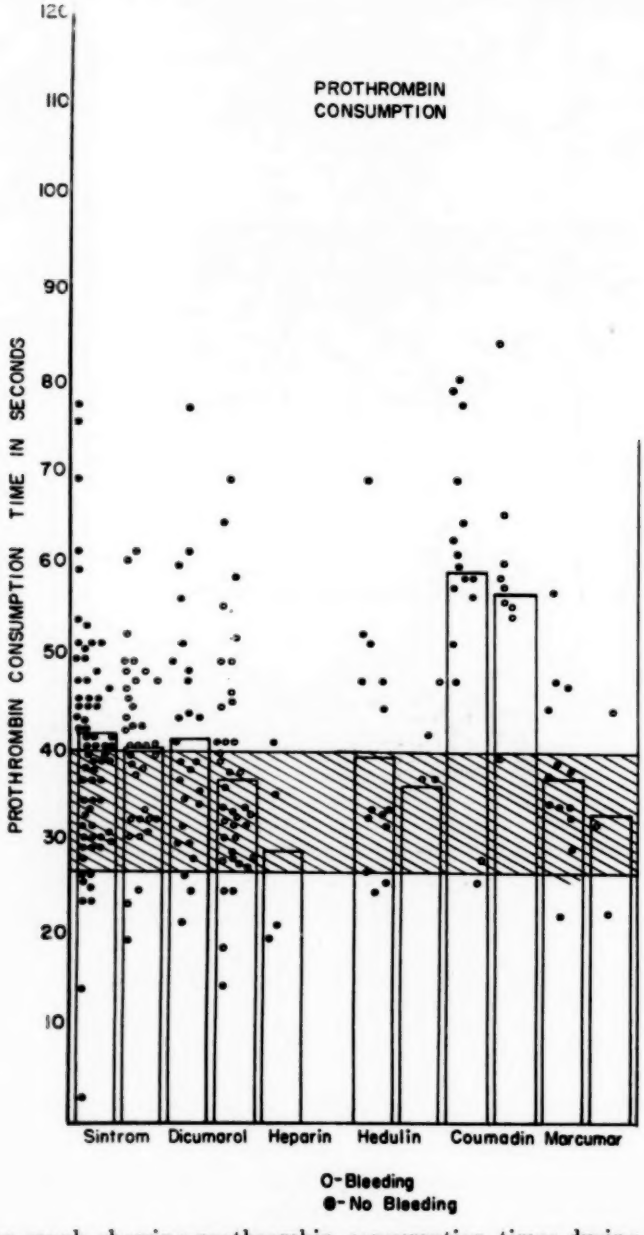

FIG. 7. Scatter graph showing prothrombin consumption times during long-term treament with various anticoagulants. For key to symbols, see legend to Figure 2.

defects in the serum of patients receiving long-term anticoagulant therapy. Combinations of sera from any two of the patients with known specific congenital defects, added in one-third volume to sera from patients treated for long periods with anticoagulants, resulted in normal thromboplastin generation.

Serum proteins. Total serum protein levels and paper electrophoresis patterns were determined in 50 normal subjects and 50 patients receiving long-term

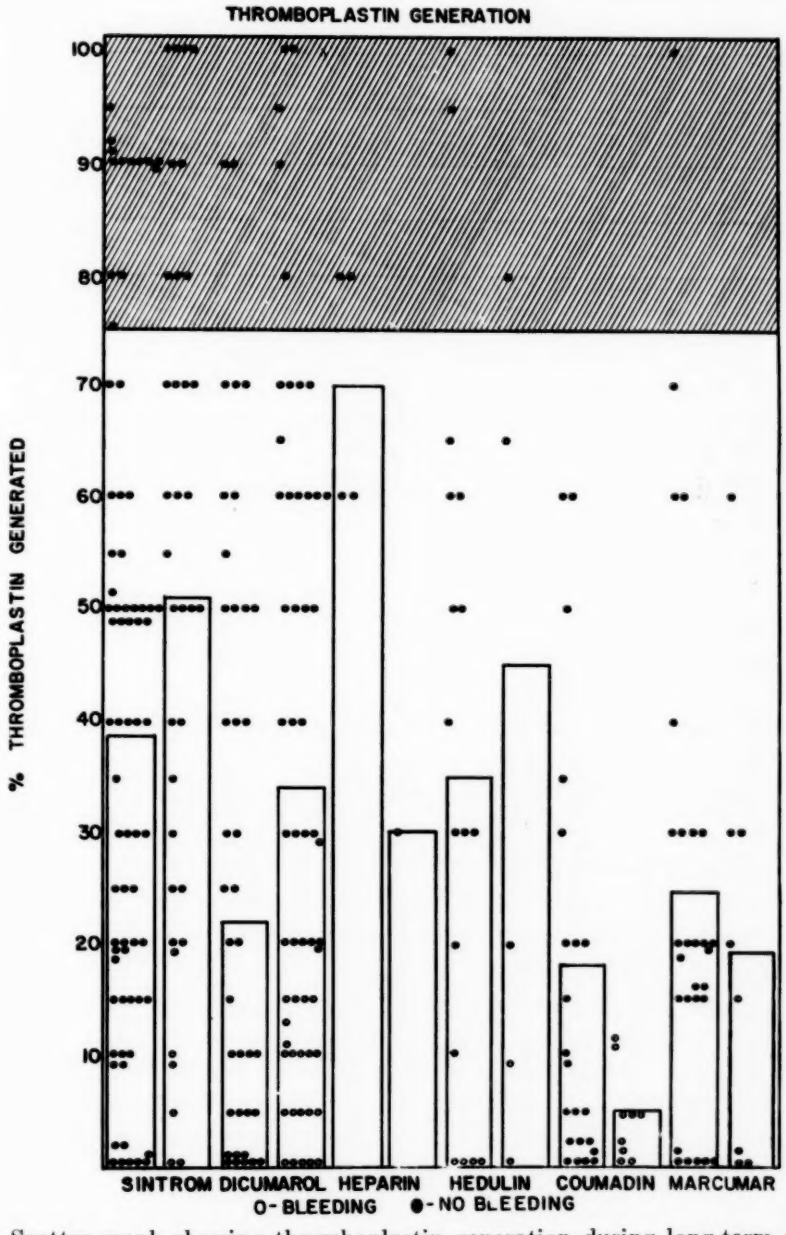

FIG. 8. Scatter graph showing thromboplastin generation during long-term treatment with various anticoagulants. For key to symbols, see legend to Figure 2.

anticoagulant therapy. No deviation from the normal range was noted. These data correlate well with the normal levels of fibrinogen mentioned previously, and are in striking contrast to the hyperglobulinemia and low fibrinogen levels generally observed in severe liver disease.

Liver function. Screening tests for liver function (*e.g.*, bromsulphalein retention) were performed on many of the patients in this series. No abnormality

in liver function was demonstrated by this technique in the patients without obvious hepotamegaly.

DISCUSSION

It is apparent that the coagulation defects produced by all the oral anticoagulants were similar (19). Prothrombin values obtained with the two-stage method paralleled those obtained with a one-stage method. There appeared to be no correlation between the extent of the coagulation defect and any past history of bleeding in the patient. These findings are in conflict with a previous report of Johnson *et al.* (20) which indicated that Marcumar[6] did not affect factor IX (PTC). However, the methods for determining the level of PTC were different in the two studies and this may be the explanation for the lack of similarity in findings. In general, it is thought that the thromboplastin generation test is a more sensitive indicator of the factors involved. Although the thromboplastin generation test is probably the best method at the present time for demonstrating defects in the first stages of coagulation, its mechanism is complex.

The striking difference in the coagulation defects produced by various oral anticoagulants compared to that produced by heparin is worthy of note (Figs. 2–8). Heparin acts primarily as an inhibitor of all coagulation reactions, whereas oral anticoagulants prevent the synthesis of the various factors involved in coagulation.

That previous histories of hemorrhage could not be correlated with the type of coagulation defects produced in patients by prolonged anticoagulant therapy may be related to the fact that the patients were not bleeding when the tests were made.

The finding of a decreased level of Hageman factor in patients receiving oral anticoagulants is interesting. Estimation of its importance in hemorrhage is difficult because the patient in whom the Hageman factor deficiency was first described had no clinical episodes of bleeding, although he had a coagulation defect similar to that associated with hemorrhagic diathesis. Presumably, this factor is not involved in the bleeding of patients receiving long-term anticoagulant therapy. Deficiencies of Factor IX (PTC) and of the Stuart-Prower factor (21) are known to be associated with clinical bleeding, and depression of these factors seems to be related to the bleeding episodes recorded in patients treated for long periods with anticoagulants.

In a recent report (22) Finkbiner *et al.* identified the coagulation defects in patients with severe liver disease. Some striking differences are evident when these data are compared to those on the patients in our anticoagulant series. In the patients with severe liver disease there was a depression in Factor V (accelerator globulin), fibrinogen and platelets, and often in the levels of serum proteins (especially albumin), whereas this was not noted in the patients receiving long-term anticoagulant therapy. Among the patients with liver disease, many were unresponsive to the administration of vitamin K, whereas there was a prompt response in the patients treated with anticoagulants.

[6] Liquamar, Organon Inc., Orange, New Jersey.

Studies are in progress to determine the types of coagulation defect that occur while patients are bleeding from anticoagulant therapy.

SUMMARY

In 300 patients studied, long-term anticoagulant therapy produced a depression of prothrombin, Factor VII, Stuart-Prower factor, Hageman factor and PTC factor. The extent of the coagulation defect was not related to any clinical history of bleeding. Definite differences in the coagulation mechanism were noted in patients with severe liver disease compared to patients receiving long-term anticoagulant therapy.

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SECURITY IN OLD AGE: ITS PHILOSOPHICAL BASIS

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In considering the needs of old people, it is not uncommon to point out how necessary is a sense of security to their happiness. It is, however, less common to mention the kinds of security which old people require or to discuss the sources from which this security may derive. Security is an important factor in happiness at any age—not indeed the greatest factor, but one which underlies most of the other needs. In older people these include a valid purpose in life, the respect of fellow beings for their personalities, some voice in ordering their own lives and an ability to exercise the right of choice. Such other rights, as privacy and the enjoyment of personal possessions (both of which are sometimes denied to old people living under institutional conditions), are included in the right of respect for personality.

The need for security in childhood and during working years has been fully realized by child and industrial psychologists. Thoughts on old age, however, are much less concrete and it is too often assumed that because old age is inherently insecure, efforts to promote a feeling of individual safety are of no importance. A dispassionate consideration of security as a life-problem seems therefore worth while.

THE STATE AND THE NATURAL LAW

A great deal is known about the kind of security afforded to the destitute sick in England in pre-reformation times through the patient research of Miss M. R. Clay (2). Although the standard was evidently uneven and varied from decade to decade, the organisation of the mediaeval hospitals which served as places of refuge was well controlled and the over-all picture is a favourable one. While medical and social needs were being provided, spiritual needs were not forgotten and the religious life of the little communities was blended with their other needs. They were maintained by the religious orders, and the gap left by the dissolution of the monasteries has never since been entirely filled.

The Welfare State as envisaged in Great Britain during the last war set out to provide security "from the cradle to the grave." Such a fantastic proposition could not have been expected to convince any serious thinker, though there were and still are many who were impressed and who had need to be reminded of the landowner in the Gospel who resolved to pull down his barns and build larger until God said to him "Thou fool, this night thy soul shall be required of thee." Apart, however, from the over-riding insecurity of life itself, the things the Welfare State Offers are, in themselves, incapable of providing the kind of security most necessary to the individual. The material things it sets out to

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guarantee (*i.e.*, food, shelter and medical care) are unfortunately incapable of providing more than temporary satisfactions. Twentieth Century experience of the Poor Law and Public Assistance in Britain should at least have taught us that material comforts of feeding, shelter and routine bodily care can only give some form of minimal security for the body, while the mind, which is incomparably the more important, can only be reached by those things that money cannot buy. It has become, in fact, abundantly clear that if only the material requirements of old people are supplied, at the expense of their psychological needs, then senile disintegration and dementia result. To supply the body, and at the same time to neglect the mind and spirit is thus a means not of providing security, but destroying it.

As the conduct of our own lives and our relations to others is, whatever our religious views may be, based on the Natural Law, it is worth while considering briefly what bearing this has on organized action to provide for the more needy of our fellows. The Natural Law which antedates Christianity and which binds all men because all men have been created, concerns itself with relationships between man and man, as well as the relationship of a man with his Creator. The sacredness of life and the responsibility of men for their fellows derive directly from the Natural Law. The association of men into communities and states does not vary the Natural Law, for the primary function of the State is to enable man to fulfil his obligations more conveniently and to impose effective restraints on unsocial individuals whose selfishness might prejudice the welfare of the many.

When the responsibility of man for his own affairs and those of his family is accepted, one can logically deduce that any arrangement of convenience which man may make (such as forming a "state" for government) cannot release him from the duties to which he is bound. Government exists to defend the defenceless and succour the needy who cannot help themselves and have no one to relieve them. As Paul Crane, S.J. (3) has pointed out, its task "is essentially subsidiary. It is meant to assist and encourage, but never to impede the responsible initiative of individual citizens, and lesser associations within the civic community."

The requirement of the Natural Law that man shall be fully responsible for his own support and that of his dependents places a limit on what the State may legitimately do in this respect. The State's warlike role is to organize and direct the manpower of the commonwealth for its protection. This does not mean that it would be, for instance, legitimate for the State to hire foreign mercenaries to do its fighting. In matters of social welfare, its duty is to encourage men to be responsible beings, to stimulate them to thrift, to help them provide for the future and to assist in caring for the sick and needy of the community. In times of stress, the State may legitimately take over the responsibilities of the individual, but should revert to its subsidiary function when the emergency is past. All this is based on the assumption that man is a responsible being. The fact that he often fails to behave in a responsible manner is not an adequate reason for the State to assume as a long-term program the responsibility which a mi-

nority of individuals shirk. Man is fundamentally responsible, and those who fail in this respect are in theory capable of being educated or civilized to a responsible outlook. The principle of "subsidiarity" again applies here; the State fulfils a more worthy function in educating man to full responsibility than when she takes upon herself the responsibilities which are rightly his.

UNDESIRABLE EFFECTS OF THE WELFARE STATE

It is not surprising that the denial of a basic moral principle should be attended by unfavourable results. Mention has already been made of the condition of the sick and aged in British Public Assistance Institutions before 1949. Conditions in these places, which also served as hospitals for the aged and infirm, have been described by Sir Arthur Thomson (9): they show what can happen when the general public cease to have any interest or sense of personal duty regarding what Government is doing. We are bound to recognise a similar danger in Government's assumption of responsibility on so wide a scale as envisaged in the Welfare State, that the sense of personal and family responsibility will decline.

So far as family responsibility is concerned, the evidence at present is equivocal. Modern conditions have made it increasingly difficult for families to do their duty to their aged relatives. Many dutiful children and families are today bearing a burden of care which is unreasonably great and which is interfering with a proper development of their lives. The reason for this is complex. The change in population structure, with a decreased birth rate early in this century following upon an abnormally high one on the preceding years, and the improvement of the health of the race have resulted in an alarming increase, actual and proportionate, in the number of persons over 60 years of age. Population migration has increased the disparity, so that the number of old people who have no relatives outside their own age-group is supplemented by those whose children have moved away from the family home for reasons of rehousing or employment. Other factors include the inadequacy of modern houses to accommodate the three-generation family, the phenomenal fall in the value of savings in the last forty years, and the scientific and technical advances which have deprived the older generation of the value of their technical experience, previously one of the assets of old age. On the psychological side, the young are being continually assailed by discouraging propaganda, to the effect that the aged are a burden on the community and that it is the State which should be responsible for them.

In spite of these adverse factors, many families and individuals are making heroic efforts to do their duty. On the other hand, a considerable proportion are accepting, and spreading in self-defence the doctrine that it is for the State to provide for the aged, and to lift the burden from the shoulders of the young. Such attitudes have always existed, and it is difficult to tell whether they are increasing. Nor can we say whether more families would accept their responsibilities if their genuine burdens could be lightened. It is probable that they would, although of this there is no certain proof. It is, however, becoming evident that we have reached, if not the edge of a precipice, at least the top of a steep

slope. If we do not check our steps we may, at least in Britain, find ourselves rolling down with increasing momentum into a condition of irresponsibility and complete dependence on the State.

That this process is beginning suggests that the denial of the principle of subsidiarity is producing some unfavourable effects. Other bad results include the crippling cost to the community, in terms of money and manpower, of the State's method of relieving need. For example, a simple case of old age frailty, maintained at home by family and neighbours with some help from organized community services, generally costs less in money and man-power than if that person were admitted to a residential home run by Government. Similarly, the cost of a "voluntary" old people's home, both in capital and maintenance charges, is frequently less than that of a statutory home, and the disparity would be even greater if more private individuals would give some of their free time to help in the organisation. These two problems of cost and personnel are preventing adequate provision of old people's services and it is at least worth considering whether shortages in finance and man-power are inevitable, or whether they are merely inevitable under State control. In Britain it is not customary to think of the lower-paid income groups as contributing more to the Welfare State than they receive in return, and yet the Oxford economist, Mr. Colin Clark (1), is able to state that "the manual-working family would be better off if it provided for its own security, instead of being forced, as it is today, to rely on the State," and furthermore that to finance social services out of taxation "makes them cost about half as much again as they would if we paid for them ourselves." This is additional evidence that the real threat to security is a form of State control which is contrary to the Natural Law.

It is therefore possible to conclude that security deriving from a Welfare State is both a snare and a delusion, that the things the State provides can never be available in the quantities required by the demands that it creates in so doing, and that even the things which it offers as the basis of security can only satisfy the physical side of nature, leaving the more important mental aspects entirely unprovided for.

THE BASIS OF SECURITY

Our approach to this problem has been, so far, largely destructive, and it is now necessary to consider what kind of security an old person needs, and how it can best be provided. Fundamentally his security derives from the world immediately around him, and his knowledge that people are willing to share with him the bare necessities of life, enjoyed by the remainder of the social group. By this provision, his physical needs are met as well, to some extent, as his mental needs which are satisfied by the respect which the community thus pays to his years. The importance of psychological satisfactions was expressed one hundred years ago by Robert Browning when he wrote "We live by admiration, love and praise," thus indicating in simple terms that equanimity depends on what we now learnedly call the "psychological defences." That satisfactions in old age depend on human relationships rather than on the

mechanical provision of human needs may be a disturbing thought to some people who find it easier to press for an increased old age pension rather than to enter into human relationship with any old person.

The vulnerable position of the aged can be best understood when we consider the origin of satisfactions during working years. They arise from capacity to earn, professional and craft skills, and from the good esteem arising from satisfactory family relationships. Failure to achieve one or more of these can be compensated by success in the others, while a valid religious faith can compensate for failure in them all. At the age of retirement an entirely new "interior" situation may develop, adaptation to which may greatly strain the aging personality. Work satisfactions are withdrawn, financial restriction commonly ensues, home life and the circle of friendship become contracted through the marriage of children and by bereavements, and the popular esteem which the community gives to a producer is changed to the equivocal approach made to a noncontributor. Women are less hardly hit than men, as for them, even in old age, the battle of life still goes on—they still have to make "both ends meet," to provide and cook the food and keep their men contented. The wife's prime role as housekeeper thus remains intact even when her efficiency begins to fail, and this may be fundamental in preserving her from senile dementia, so long as she has a house and a husband to manage.

As important as the interior situation in which the old person finds himself, is the exterior environment, created by the attitude of the community towards old age—what we may conveniently call "the climate of old age." This has varied from era to era and from one civilisation to another. In the Western World, the climate of old age has recently deteriorated, with the change from a patriarchal type of civilisation to one where youth-values are overemphasized at the expense of those of older citizens. Leo Simmons (8) in his "Role of the Aged in Primitive Society" tells how in primitive civilisations the aged retained their power and position. When cultural and religious values failed to provide old age with respect derived from its experience, the old person could, and did, sell his knowledge and craft technique for beasts or corn—so much of one in exchange for so much of the other—while in other tribes the aging magician bartered his magical powers on the same lines. His assets were thus tied to the cost of living. When all else failed, the aged person's proximity to death could be turned to good account, as he was approaching a higher plane of existence from which he could effectively aid or harm those who had pleased or displeased him in this world.

Religious sanctions are, however, no longer applicable in the Western World in the middle Twentieth Century, and old age must now rely on its intrinsic value to the community in order to retain respect. One of the main difficulties of the present situation lies in the fact that the meaning of old age has been very largely forgotten, not only by the young in their preoccupation with scientific advances, but even forgotten by the old themselves.

In a word, security depends largely upon a feeling that one is wanted. To feel wanted, however, one must be able to convince oneself, as well as other

people, that one is worth wanting. This at once raises the vital problem of the intrinsic value of old age to the individual and to the whole community. In his essay, "The Stages of Life," C. G. Jung (4) has pointed out that "a human being would certainly not grow to be seventy or eighty years old if this longevity had no meaning for the species to which he belongs." This is an important approach in view of the diminishing material assets of old age. The contribution made by the older generation to life is much greater than is generally imagined, and many people up to the age of 75 remain as contributors to the stability of civilisation, as J. H. Sheldon (7) has recently pointed out. Many pensionable people of both sexes continue taking an active part in industry and other employments; even if they do the less strenuous work, at least they free younger workers for more active roles. By taking an important share in the daily care of their grandchildren, they ease the burden on young mothers and release others for employment in industry. The recent war showed the value of older people as a labour-pool, on which industry is forced to depend in times of emergency. By their very presence in the community, they stimulate younger people to save for their own old age and thus help to balance the national budget. The place of the old in acting as preservers of cultural and religious values of ths group has been insufficiently appreciated; by their attitude of tolerance and wise guidance they can do much to preserve the integrity of the home for the rising generation. The sum of these contributions is considerable and is enough to warrant us to look upon healthy old age as a national heritage, as vital to the country as a generation of strong active children.

THE INDIVIDUAL VALUE OF OLD AGE

We must, however, guard against thinking of old age exclusively in terms of its community worth. Its prime value is for the individual. Old age is a stage of life as essential for the maturing of the personality as adolescence or middle-age; without it, the life-cycle cannot be considered complete (Rudd (5)). If we look on old age as a normal stage in life, we can postulate for it the characteristics which mark other life-stages, *i.e.*, lessons to be learned, dangers to be faced and specific contributions to the life of the community. Taken together, these contributions can be called the "work of old-age." Should an individual die prematurely, this work may be unfinished, and the community suffers accordingly. An example of this is given by Great Britain and France, both of whom are at present suffering on a nation-wide scale from such a deprivation due to the losses of their young men in the 1914 war. The lessons and hazards of the period are concerned with the person's ability or inability to "grow up" into old age, relinquishing the attitudes characteristic of maturity, in favour of those proper to a new stage in life. In youth and middle-age, it is right that men and women should be concerned with the instincts of power and reproduction. In old age, these belong to the past, and the person who allows himself to be still guided by them, does so at his peril. It is the ability to live without the material aspirations which seem so important in earlier years, which characterises an old age which is psychologically healthy. In Jung's (4) words, "we cannot live the after-

noon of life according to the program of life's morning—for what was great in the morning will be little at evening, and what in the morning was true, will at evening have become a lie." If this be so, the captain of industry who remains at the helm throughout his seventies and whose business successes are won at the cost of diminution of personality is in his way as abnormal as Tennessee Williams' "Baby Doll"—and the result is likely to be as great damage to the soul.

This is about as far as the argument can be advanced unless we are prepared to trespass on the ground of religious philosophy. Life is essentially a purposive thing and every one of its stages has an objective which by definition must lie in the future: adolescence looks forward to the glittering prizes of maturity, while people of middle age may eagerly anticipate the tranquility and rest of a well-deserved retirement. That this principle applies to old age too has been largely forgotten today, and many old people are sick, mentally or physically, because they have forgotten that old age has its goal and its work in achieving that goal. Jung (4) has summarised this thought by saying that "it is hygienic . . . to discover in death a goal towards which one can strive." It is, in fact, a psychological necessity (leaving aside any considerations of religious faith) for healthy happy old age to believe in and to prepare for an after-life. The climax of living is thus placed, not in the noontide during the active productive phase, but in the hereafter, so that life throughout all its stages can be directed towards a single goal.

It is perhaps not over-simplifying the matter if we say that the purpose of the closing years of life is to learn renunciation, just as the purpose of early life is to learn how to acquire and use. Renunciation is certainly forced on us as life passes its zenith, renunciation of our special senses of sight, sound and taste, renunciation of bodily activity, of family and friends, and of the interests which make life sweet. Lessons of the highest spiritual value, impossible to learn during the acquisitive phase of life, now come within our scope. The monastic ideals of poverty, chastity and obedience, which many great men have found to be the gateway of spiritual achievement, enter the lives of many old people for the first time. Even when their imposition is resented, the lesson may be learned and the soul accordingly made readier for heaven. The positive result of the experience was indicated by the great Spanish mystic, St. John of the Cross (6), when he wrote:

> "Now guard I no flock, nor have I now other office
> For now my exercise is in loving alone."

Failure to learn renunciation is, however, inevitably accompanied by spiritual impoverishment, described by St. John of the Cross in the lines

> "I live but no true life I know
> And living thus expectantly
> I die because I do not die."

This is a penetrating comment on the mental poverty of those who resist the normal process of growing up.

PRODUCING A FAVOURABLE "CLIMATE" FOR OLD AGE

In spite, however, of the very real benefits able to be gleaned from the disabilities of old age, the latter years of life can only be of their maximum value to the development of personality if they are accompanied by health of body and vigour of mind. With this in view, it is plain that it is our duty to preserve the highest standard of health, both for ourselves and others. It is also part of our duty to preserve our own health and independence so that we shall not be burdensome on the community in our declining years.

Healthy old age should be thought of, not as an ideal, but as a normally attainable thing, and an unhealthy old age as abnormal, unnecessary and preventable. To have the best chance of being mentally well in old age, old people need to be surrounded by the right environment, and in this perhaps lies the great bulwark of security.

Bodily health in old age is a very desirable thing but, even less than in earlier years, it is not an end in itself, as may be seen in the case of healthy old men in institutions who sit unoccupied and uninterested throughout the long hours of the day. Activity of the body is necessary in order that the mind be kept active and alive. Having sound feet is insufficient, if your legs have no place of interest to which to take you, and thus chiropody services are inadequate unless they form part of a program designed to keep the person happily integrated with the life of the community. To obtain this, the attitude of the community needs to be sympathetic and understanding.

This brings us to the heart of the problem of security in old age—how to produce a national climate for old age, based on understanding of what age means, and sympathetic with its needs. A feeling of identification between the community and its old people is very important, as it is the basis of personal preparation for retirement. In these days when nearly every house is reached by radio or television, mass adult education has become possible on a scale undreamed of previously. These media are showing great interest in the problems of aging, though an interest which is more than passing is required. It is also most important that, if the listening and viewing publics are being asked to think, their thinking should be directed along the right lines. If, for instance, they are to be taught by television that they have no reason to fear for the future, since an omnicompetent state will provide for their care, then we are perpetuating the delusion of safety where no safety exists.

THE NEED FOR PERSONAL SERVICE

Some form of summing up seems necessary. In the first place, security lies in a proper appreciation of the value of old age, to the individual as well as the community, together with an assessment of its dangers. Secondly, to maintain security we must succeed in building up an atmosphere of charitable understanding for those who are old and to render them all the personal service within our power. The methods of St. Vincent de Paul and his disciple Saint Louise de Marillac (who founded the Sisters of Charity) are most deserving of study, as

they are so relevant to the needs of today. Workers with a sense of vocation are needed in all the fields of old people's care, whether as nurses, home helpers or as workers in residential homes. The religious orders, too, need support in the great work they are doing under difficulties; more financial help and above all, more vocations. We need more efforts sponsored and run by charitable societies, of a religious or social nature, for old people's care. In Britain at least, the running costs can be reclaimed from the local Government funds; what is needed is the original outlay, and the personnel to maintain the work. The Western Nations have both the money and the manpower. What is sometimes lacking is the will to use them on the right things. For every call to carry out charitable works on the grand scale, through the agency of the religious orders, there is a call for thousands to turn their energies from luxury professions and trades to the daily service of the more needy of their fellows.

Thirdly, there is a lot that must be done to educate the public as well as ourselves, on the right attitudes towards old age, both on the personal plane and from the national point of view. When we ourselves can resist the politician's bluff that the social welfare schemes of any political party can afford any measure of real security, then we shall have taken the first step in convincing others as to where security lies. These problems need thought and study. If complete control by the State over our lives is to be prevented, we shall have to be ready, sooner or later, with alternative plans for social security. This provides an immense field of study for individuals and organisations who value liberty and personal responsibility.

The whole problem is a religious one. For old people who are parents, security depends upon a family brought up in the knowledge and love of God. For those who are childless, security comes from living in a community which has the broadest sense of its family responsibilities. Real security, however, dwells in something deeper still. It lies in the love of God for the individual soul, especially at a time of earthly trial. Only when we see old age in this light will we be able properly to orientate ourselves towards it, and to give comfort to all those who turn to us in their needs.

SUMMARY

Security in post-retirement years depends on a proper appreciation by the aged themselves and by the younger age-groups of the meaning of old age, both for the community and for the individual. Such an appreciation will produce a climate for old age which will be both sympathetic and conducive to positive mental health.

The concept of the Welfare State which takes upon itself the responsibilities which by tradition have rested on the family group (as by the Natural Law they properly should) is prejudicial to real security and may ultimately destroy it.

There is a great need for professional as well as public education in these matters, together with an awakening of a sense of family responsibility in the broadest sense, to include all needy members of the community.

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CLINICAL EXPERIENCE WITH CHLORPROPAMIDE AND COMPARATIVE EVALUATION WITH TOLBUTAMIDE

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The use of oral hypoglycemic agents, at least in the treatment of maturity-onset diabetes, is now generally accepted by the medical profession. This radical innovation in the treatment of possibly half a million or more diabetic patients in the United States alone has been instituted despite the fact that many important questions about these drugs remain unanswered. Certainly not the least of the riddles are the specific mechanisms of action and the effect of long-term therapy on the natural history of diabetes, particularly in regard to the incidence and type of vascular complications.

Despite this lack of final and complete knowledge, and judging only by the empirical yardsticks of diabetic control and lack of toxicity or side-effects, at least two oral hypoglycemic agents, chlorpropamide and tolbutamide, appear to be withstanding the test of time in a favorable and commendable manner. This is true, at least, when their use is properly restricted to that segment of the diabetic population in which the disease is mild but still requires modest doses of insulin for control. It must be emphasized that these compounds provide the physician with such an easily invoked and greatly desired mode of therapy that only those with real foresight and firm conviction will be able to restrict the use of such drugs to properly indicated and controlled cases and thus prevent dangerous abuse. The control of glycosuria with oral hypoglycemic agents in a grossly obese diabetic, or the permission of poor control in a more severe diabetic while receiving such medication merely because of convenience, are examples of dangerous abuse.

With the knowledge gained by pooled experience in administering these drugs in large numbers of cases over extended periods of time, even the most cautious physician need feel few qualms about using them on an empirical basis. The foundations of medical practice have long been established upon probability considerations, because practitioners know that in this art certainties do not exist. By this rationale, the considerable benefits to be obtained from the proper use of oral hypoglycemic agents in many diabetic patients need not be denied them while the final answers to specific metabolic effects are being sought.

To extend these benefits and add to the pool of clinical experience, chlorpropamide, one of the newer sulfonylurea drugs, has been in use on the Metabolic Service at Harlem Hospital, New York City, for the past year. Prior to this, tolbutamide was the only oral hypoglycemic agent under evaluation there. It

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TABLE 1

Chlorpropamide Study

Patient No.	Sex/Age	Previous Rx and Daily Dose (units)	Initial Fasting Blood Sugar (mg./100 ml.)	Duration of Rx	Last Fasting Blood Sugar (mg./100 ml.)	Chlorpropamide Maintenance Dosage (mg. per day)	Results*
1	F/52	NPH 40	290	8 mos.	286	1000	SF
2	F/50	NPH 30	160	12 mos.	135	200	E
3	F/59	NPH 40	230	5 wks.	88	500	E
4	F/39	NPH 45	200	4 wks.	221	500	DC-J
5	F/51	NPH 45	125	2 days	560	1500	PF
6	M/55	NPH 20	79	11 mos.	130	100	E
7	M/43	NPH 25	145	12 mos.	120	100	E
8	M/72	NPH 20	90	12 days	↓ 50	250	DC-H
9	M/57	NPH 20	206	12 mos.	150	250	E
10	F/55	NPH 10	126	2 wks.	180	500	DC-G
11	F/65	—	175	5 wks.	130	200	E
12	F/63	Diet	240	10 mos.	164	50	E
13	F/60	NPH 20	250	10 mos.	130	250	E
14	F/56	NPH 15	170	9 mos.	138	250	E
15	F/52	NPH 10	213	9 mos.	140	250	E
16	M/34	Lente 30	168	10 mos.	164	750	E
17	F/45	NPH 20	195	11 mos.	250	500	SF
18	F/55	NPH 15	316	10 mos.	126	100	E
19	F/58	NPH 25	220	4 wks.	244	750	PF
20	F/58	NPH 15	175	9 mos.	141	250	E
21	F/60	NPH 20	200	9 mos.	88	50	E
22	F/42	NPH 20	165	7 mos.	170	50	G
23	F/60	NPH 20	155	9 mos.	150	500	E
24	F/59	NPH 30	215	9 mos.	123	250	E
25	F/60	NPH 20	141	8 mos.	138	200	E
26	F/50	New—Diet	300	3 mos.	79	Discont'd	E
27	M/50	Diet	180	2 wks.	244	500	PF
28	F/52	New—Diet	250	3 wks.	150	500	E
29	F/79	Diet	215	9 mos.	160	250	E
30	F/57	NPH 20	220	3 wks.	225	500	PF
31	F/67	NPH 20	150	3 wks.	112	125	E
32	M/56	Diet	300	3 wks.	310	500	PF
33	F/59	Diet	250	2½ mos.	250	500	PF
34	F/71	Diet	265	7 mos.	360	250	SF
35	M/69	NPH 30	159	6 mos.	104	125	E
36	M/51	NPH 15	192	5 mos.	140	250	E
37	F/77	NPH 15	175	4 wks.	123	125	E
38	M/68	NPH 25	155	6 mos.	134	250	E
39	F/51	NPH 25	221	6 mos.	164	125	E
40	F/48	NPH 15	274	5 mos.	134	100	E
41	F/62	NPH 30	106	5 mos.	145	250	E
42	M/60	NPH 30	150	3 mos.	150	500	E
43	F/72	NPH—	275	3 mos.	88	125	E
44	M/61	Diet	210	4 mos.	134	250	E
45	F/56	Diet	210	4 mos.	98	50	E

TABLE 1—*Continued*

Patient No.	Sex/Age	Previous Rx and Daily Dose (units)	Initial Fasting Blood Sugar (mg./100 ml.)	Duration of Rx	Last Fasting Blood Sugar (mg./100 ml.)	Chlorpropamide Maintenance Dosage (mg. per day)	Results*
46	F/60	NPH 20	126	4 mos.	145	250	E
47	F/49	Diet	206	3 wks.	110	100	E
48	M/48	NPH 15	205	6 mos.	122	125	E
49	F/68	NPH 15	230	5 mos.	145	125	E
50	F/84	Diet	175	2 mos.	106	100	E

* Key E = Excellent. SF = Secondary failure. G = Gastro-intestinal symptoms.
G = Good. PF = Primary failure. D = Dermatitis.
F = Fair. DC = Discontinued. J = Jaundice.
H = Hypoglycemia.

Note that all side-effects occurred in the first 10 cases.

seemed appropriate, therefore, after almost two years, to analyze and compare all cases which had been treated uniformly with either drug by the same observer.

PROPERTIES OF CHLORPROPAMIDE AND TOLBUTAMIDE

Chlorpropamide[1] is an arysulfonylurea with the chemical name 1-(p-chlorobenzenesulfonyl)-propylurea. It is rapidly absorbed from the gastro-intestinal tract and exerts a hypoglycemic effect within one hour; this effect becomes maximal in three to six hours and persists for at least twenty-four hours (1). Chlorpropamide is excreted slowly in the urine as the active hypoglycemic material since, unlike tolbutamide, it is not deactivated in the human. The half-time of its disappearance from the serum after a single 0.5-Gm. dose is about thirty-five to forty hours (2–3), or about ten times longer than that of tolbutamide (3). It has been reported to have up to six times the hypoglycemic potency of tolbutamide (1).

The chemical designation for tolbutamide[2] is 1-butyl-3-p-tolylsulfonylurea. It, like chlorpropamide, is an orally active hypoglycemic agent (4). Since both are arylsulfonylureas, presumably their mechanisms of action are similar, differing only in degree. Tolbutamide also produces a rapid fall in the blood sugar level which, in responsive diabetics, usually becomes maximal in five to eight hours. Doses in excess of 3 Gm. usually induce no greater fall in the blood sugar level than do doses of 3 Gm. or less. Tolbutamide undergoes oxidation, presumably in the liver, to an inactive carboxyl derivative. Its excretion is much more rapid than that of chlorpropamide. As much as 75 per cent of a dose appears in the urine within twenty-four hours as an inactive metabolite which interferes with the usual tests for albuminuria (5).

[1] Supplied as Diabinese by Pfizer Laboratories, Brooklyn, New York.
[2] Orinase, Upjohn Co., Kalamazoo, Michigan.

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CLINICAL MATERIAL AND METHODS

In this study 85 diabetic patients were selected from the metabolic wards and from the Diabetic Outpatient Department of the Harlem Hospital, New York. Of these, 50 were given chlorpropamide for twelve months, and 35 were given tolbutamide for twenty-one months (Tables 1 and 2).

The average age of the patients receiving chlorpropamide was 58.3 years, and the average duration of their diabetes was approximately five years. The average age of the patients receiving tolbutamide was 60.6 years, and the average duration of their diabetes was 7.6 years.

The criteria for selecting these patients were:

1. The patient must have been at least age 40 at the time of onset of the diabetes ("maturity-onset" diabetes).
2. The insulin requirement must be no more than 30 to 40 units daily.
3. The diabetes cannot be controlled by diet alone.
4. The patient is not grossly obese.
5. No failure during previous therapy with oral hypoglycemic agents.[3]

If a patient was "over-controlled" with insulin therapy or excellently controlled with 10 to 15 units of insulin, he was not accepted for trial until it was clearly established after several weeks of either a gradual decrease or complete discontinuation of insulin that diet alone would not suffice. This precaution eliminated a surprisingly large number of patients who remained aglycosuric and adequately controlled with diet alone *after* discontinuation of the daily dose of insulin. Undoubtedly, all of these excluded patients would have had an excellent therapeutic response to either medication!

The first 10 patients treated with chlorpropamide were hospitalized and kept under close clinical and laboratory observation. The next 40 cases were from the diabetic clinic. In accordance with the initially recommended starting dose, the first 10 patients received 500 mg. of chlorpropamide three times daily. At that time the optimum dosage and duration of action had not been fully determined. As indicated by increasing clinical experience, the starting dose subsequently in almost every patient was reduced to 500 mg. once a day, after breakfast. Some of the elderly diabetics with mild symptoms received a daily starting dose of 250 mg.

Cases were classified as primary or secondary failures if they could not be initially controlled or subsequently maintained with 500 to 750 mg. of chlorpropamide daily. A minimum period of three to four weeks of chlorpropamide therapy was required for inclusion of patients in the study, since this period of time is considered necessary for evaluation of the initial response, unless severe loss of control intervenes.

The tolbutamide group consisted of 35 clinic patients. The starting dosage was usually 1 Gm. three times daily for the first day, followed by 1 Gm. twice a day for one week, or 0.5 Gm. three times daily for one week. In some instances, to avoid dosage confusion by some elderly patients, 1 Gm. was given twice daily on the first and subsequent days. Following this the dosage was maintained or decreased according to the laboratory findings. For economic reasons it was not considered practical to attempt to control patients with tolbutamide if 1,500 to 2,000 mg. daily did not suffice after the 3,000-mg. loading dose. Accordingly, patients who did not respond or could not be maintained with this maximum dosage were classified as primary or secondary failures.

All clinic patients were seen initially at intervals of one or two weeks, according to their responses. Blood sugar tests and urinalyses were carried out at each clinic visit. No new or additional dietary instructions were given unless specifically required.

Results in both chlorpropamide and tolbutamide patients were arbitrarily classified as "excellent" if the usual fasting blood sugar level was 165 mg. per 100 ml. or lower; "good" if it was between 166 and 179 mg. per 100 ml.; and "fair" if it was between 180 and 199 mg. per 100 ml. With or without glycosuria, a fasting blood sugar level of 200 mg. per 100 ml.

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[3] Added only for the purpose of comparative chlorpropamide-tolbutamide studies.

TABLE 2

Tolbutamide Study

Patient No.	Sex/Age	Previous Rx and Daily Dose (units)	Initial Fasting Blood Sugar (mg./100 ml.)	Duration of Rx	Last Fasting Blood Sugar (mg./100 ml.)	Tolbutamide Maintenance Dosage (mg. per day)	Results*
1	F/51	NPH 30	205	3 mos.	221	1500	SF
2	F/60	NPH 20	159	7 mos.	212	1500	SF
3	F/71	NPH 40	105	14 mos.	92	500	E
4	F/52	NPH 35	95	4 mos.	95	1000	E
5	F/74	NPH 15	158	21 mos.	106	1000	E
6	F/55	NPH 20	159	5 mos.	104	1500	E
7	F/54	Diet	260	7 wks.	186	1500	DC-G
8	M/65	NPH 20	180	21 mos.	95	1000	E
9	F/63	Diet	221	5 wks.	205	1500	PF
10	F/65	NPH 30	164	3 wks.	100	1500	DC-G
11	F/42	NPH 20	141	18 mos.	215	2000	SF
12	F/53	PZI 40	165	21 mos.	115	1000	E
13	F/55	NPH 15	220	19 mos.	165	1500	G
14	F/66	NPH 20	195	5 mos.	270	1500	PF
15	M/62	NPH 25	180	12 mos.	186	2000	F
16	F/66	Diet	300	1 wk.	350	2000	PF
17	F/62	Diet	240	16 mos.	240	1500	SF
18	F/67	NPH 20	213	2 wks.	155	1000	DC-D
19	F/57	NPH 20	116	2 mos.	210	2000	SF
20	F/69	NPH 15	145	3 wks.	110	1000	E
21	F/58	NPH 20	169	3½ mos.	270	1500	SF
22	F/62	NPH 30	87	5 wks.	122	1000	E
23	F/71	NPH 40	180	3 wks.	282	1500	PF
24	M/72	PZI 25	168	3½ mos.	206	1500	PF
25	M/69	NPH 20	150	3 mos.	105	500	E
26	F/66	NPH 20	215	10 mos.	221	2000	PF
27	F/54	NPH 15	175	21 mos.	200	2000	F
28	F/54	NPH 10	130	2 wks.	240	1500	DC-G
29	F/54	NPH 20	158	4 mos.	136	1000	E
30	F/65	NPH 20	150	5 mos.	175	500	G
31	F/49	NPH 15	186	19 mos.	310	3000	SF
32	M/62	NPH 30	135	3 wks.	300	2000	PF
33	F/58	NPH 10	206	4 mos.	310	1500	SF
34	F/70	NPH 10	140	17 mos.	150	500	E
35	F/48	NPH 25	213	17 mos.	218	2000	SF

* For key, see footnote to Table 1.

or higher was considered a "poor" response. "Primary failure" denoted lack of response initially, and "secondary failure" denoted the development of resistance after a period of satisfactory response.

RESULTS

Chlorpropamide

As shown in Table 3, 38 (76 per cent) of the 50 patients receiving chlorpropamide therapy exhibited a favorable response. Thirty-seven (74 per cent)

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TABLE 3

Chlorpropamide and Tolbutamide: Comparison of Clinical Results

No. of Patients Treated with	Favorable Responses*				Failures		Average Maintenance Dose Per Day	No. of Patients Showing Side-effects
	Total	E	G	F	Primary	Secondary		
Chlorpropamide								
50	38 (76%)	37 (74%)	1 (2%)	0 (0%)	6 (12%)	3 (6%)	221.5 mg.	3† (6%)
Tolbutamide								
35	15 (42.8%)	11 (31.4%)	2 (5.7%)	2 (5.7%)	7 (20%)	9 (25.7%)	1066.0 mg.	4‡ (11.4%)

* E = Excellent (fasting sugar level below 165 mg. per 100 ml.).
G = Good (165–179 mg. per 100 ml.).
F = Fair (180–199 mg. per 100 ml.).
† Includes 1 case of jaundice.
‡ Includes 1 case of allergic dermatitis.

of these had an "excellent" response, 1 (2 per cent) a "good" response, and none a "fair" response. Of the remaining 12 cases 6 (12 per cent) were classified as primary failures and 3 (6 per cent) as secondary failures; in 1 case (2 per cent) the medication had to be discontinued because of gastro-intestinal symptoms; in 1 case (2 per cent) jaundice and severe dermatitis developed after twenty-seven days of therapy; and in 1 case (2 per cent) persistent hypoglycemia developed without symptoms.

The average maintenance dosage of chlorpropamide in 36 patients (2 were able to discontinue medication entirely) was 221.5 mg. daily—less than one 250-mg. tablet per day. In 34 patients the entire dose was given once daily after breakfast; the remaining 2 patients received 100 mg. on alternate days only.

Tolbutamide

In the 35 patients receiving tolbutamide therapy, after a longer period of observation than the chlorpropamide group, there were 15 favorable responses (42.8 per cent). In 11 of these (31.4 per cent) there was an "excellent" response, in 2 (5.7 per cent) a "good" response, and in 2 (5.7 per cent) a "fair" response. Of the remaining 20 cases, 7 (20 per cent) were primary failures and 9 (25.7 per cent) were secondary failures; in 3 cases (8.5 per cent) the medication was discontinued because of gastro-intestinal symptoms; and in 1 case (2.5 per cent) typical allergic dermatitis developed. No hypoglycemic responses were noted in any of these patients.

The average maintenance dosage of tolbutamide in the 15 responsive patients was 1,066 mg. daily, or slightly more than two 500-mg. tablets per day. All tolbutamide patients were given the medication in fractional doses, two or three times daily.

DISCUSSION

Although the typical syndrome of toxic hepatitis associated with a generalized skin rash developed in the fourth patient treated with chlorpropamide in this series (Table 1), it should be noted that the starting dose was three times that currently used and recommended by us. During the acute phase of this reaction, which lasted six days, the serum alkaline phosphatase level rose to 28.3 Bodansky units per 100 ml., the serum icteric index was 48, and needle biopsy of the liver showed intracanalicular biliary stasis. Another patient (No. 8, Table 1) in whom therapy was discontinued because of persistent hypoglycemia without symptoms was also in the initial group whose starting dosage was 1500 mg. daily. This elderly man was admitted to the ward because of a cerebral thrombosis. In retrospect, the true nature of the diabetic syndrome was never clearly established prior to his discharge. At that time he had a normal blood sugar level and was maintained with dietary therapy alone.

In considering the occurrence of secondary failure in diabetic patients receiving oral hypoglycemic therapy it should be kept in mind that the severity of the disease fluctuates to some extent in practically all cases, sometimes for obvious reasons but often for no apparent reason. Consequently, a hypoglycemic agent may be therapeutically effective during one period of life-long diabetes but fail during another more severe phase, becoming a "secondary failure." Since this resistance may occur even in mature "stable" diabetics, it is quite conceivable that some patients, after a variable length of time, may again become responsive to the medication. This apparently inherent characteristic of diabetes makes it necessary to increase or decrease the dose of any oral hypoglycemic agent periodically according to the requirements indicated by serial urine and blood sugar determinations, just as constant surveillance and change of dosage is required during insulin therapy. In 2 patients of the chlorpropamide group, therapy was discontinued after several months because diet alone was sufficient; this was done despite the fact that at the time chlorpropamide was instituted, the need for it in addition to dietary control had been clearly established. The improvement in these 2 patients must be attributed to spontaneous amelioration of the disease unrelated to specific therapy.

In some patients treated with sulfonylureas, resistance to the hypoglycemic effect can develop after some months of initially good response. In the smaller group of tolbutamide patients, who were under observation for a longer period than the chlorpropamide patients, this resistance (secondary failure) occurred in 26 per cent, under the conditions of our arbitrary dosage schedule. In contrast, these secondary failures occurred in only 6 per cent of the chlorpropamide patients (Table 3). The maximum maintenance dosage of tolbutamide was limited by economic factors to three or four tablets daily per patient, since at this level the cost was already five to seven times higher than comparable insulin dosage. The upper limit of maintenance dosage of chlorpropamide cost three to four times as much as comparable insulin therapy. One tolbutamide patient (No. 31, Table 2) in whom drug resistance (secondary failure) had developed

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after more than a year of favorable response, received a dosage of 3000 mg. (six tablets) per day without regaining the satisfactory therapeutic effect.

By the methods used, chlorpropamide produced satisfactory control in almost twice as great a percentage of patients than did tolbutamide. In addition, smaller and less frequent doses were required than with tolbutamide.

Significant untoward reactions, notably jaundice and hypoglycemia, did not occur in the 40 chlorpropamide patients studied later in the series who received much smaller doses of the drug than did the first 10 patients (Table 1). From this it appears that the frequency and severity of some of the side-effects associated with chlorpropamide may be directly related to the magnitude of the dosage. Therefore, it is important to maintain any given patient at the lowest dosage level consistent with adequate control of the diabetes. Furthermore, since the average chlorpropamide maintenance dosage in the present series was 221.5 mg. daily, it would seem that an initial dosage of 250 mg. daily might be sufficient for most patients.

In view of these highly suggestive findings, a new comparative study of chlorpropamide and tolbutamide has been initiated, in which the two agents are being compared under similar conditions, using alternate patients selected by identical criteria. The pooling of similar experiences in comparative evaluation would be of great benefit in the assessment of the current status of oral hypoglycemic agents.

SUMMARY

A clinical study of the effect of chlorpropamide in 50 patients with "maturity-onset" diabetes is presented, and compared with the effect of tolbutamide in a similar but smaller group of 35 patients selected by the same criteria.

The findings of these studies were: 1) chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent); 2) the incidence of primary and secondary failures with tolbutamide therapy was notably higher than with chlorpropamide therapy; and 3) with the dosage levels used, chlorpropamide produced as few, and possibly fewer, side-reactions than did tolbutamide.

Further comparative evaluations would be of value in the final assessment of these two clinically effective oral hypoglycemic agents.

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AMEBIASIS: A PROBLEM OF INTESTINAL SYMPTOMATOLOGY IN THE AGED

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Amebiasis is the most cosmopolitan and serious protozoan disease of man. Although the causative organism, *Endamoeba histolytica*, may live as a commensal parasite in man, certain conditions enhance the pathogenicity of the agent. Such factors may include poor nutrition, debilitating disease, poor sanitation, and degenerative diseases of the aged.

Digestive complaints are frequent in geriatric patients and may be treated without due diagnostic consideration of amebiasis, a disease that mimicks many other disorders. Both benign and serious intestinal illnesses may simulate amebiasis, which is protean in its manifestations. Also, many subclinical cases pass unrecognized (1).

CLINICAL MATERIAL

Thirty-four white patients 65 years of age and older, selected from private practice, were included in this study; there were 15 males and 19 females. The age distribution is shown in Table 1.

DIAGNOSIS

Gastro-intestinal symptomatology

The symptomatology of amebiasis is primarily gastro-intestinal (Table 2). The most frequent symptoms were abdominal distension and flatulence, which occurred in 20 and 19 patients respectively. Abdominal discomfort was a significant symptom, right lower-quadrant tenderness being present in 16, right upper-quadrant pain in 8, and tenesmus in 8.

Frank dysentery was present in only 4 cases; diarrhea was the presenting symptom in 12. However, there was recurrent diarrhea in 11, and constipation alternating with diarrhea in 7. Thus, the idea that amebiasis represents only amebic dysentery is outmoded. It is noteworthy that 12 patients had a history of recurrent "food poisoning," and 9 a history of recurrent "intestinal viral infections."

Symptoms of vague indigestion (10 cases), anorexia (11 cases), bulimia (8 cases), and eructation (5 cases) could easily have been mistaken for those of peptic ulcer, chronic atrophic gastritis, gastric achlorhydria, or carcinoma of the stomach. Gastro-intestinal x-ray examination and hydrochloric acid determinations refuted these diagnoses. Vomiting was not common, being present in only 2 patients.

No distinct hemorrhages were observed, but rectal bleeding was present in 4,

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TABLE 1

Age Distribution in 34 Patients with Amebiasis

Age Group (yrs.)	No. of Patients
65–69	20
70–79	10
80–89	3
90–95	1

TABLE 2

Gastro-Intestinal Symptoms in 34 Cases of Amebiasis

Symptom	No. of Cases
Abdominal distension	20
Flatulence	19
Vague indigestion	10
Eructation	5
Bulimia	8
Tenesmus	8
Recurrent "food poisoning"	12
Recurrent "intestinal viral" infections	9
Right lower-quadrant tenderness	16
Diarrhea	12
Dysentery	4
Recurrent diarrhea	11
Constipation alternating with diarrhea	7
Anorexia	11
Pruritis ani	9
Rectal bleeding	4
Vomiting	2
Right upper-quadrant pain	8
Bloody mucus in stools	9

and the stools contained bloody mucus in 9. Pruritis ani was extremely troublesome in 9 patients, but subsided after anti-amebic treatment.

Systemic symptomatology

Chronic amebiasis presents many secondary systemic symptoms which may overshadow the intestinal or primary complaints. Many patients may remain asymptomatic for long periods of time. The nonspecific or constitutional symptoms are listed in Table 3; it is obvious that lassitude, vertigo, weakness, dyspnea, cardiac arrhythmias, and paresthesias may confuse the clinical picture. Arthralgias and myalgias are frequent enough to be striking. Cardiovascular symptoms of chest pain, cough, dyspnea, and cardiac irregularity may be present, but subside with amebicide therapy. Neurologic symptoms such as headache, vertigo, and paresthesias may present diagnostic problems. Weight loss was noted in only 5 patients of our series. Fever was present in only 4. Severe urticaria in 2 elderly patients cleared with amebicides, and did not recur.

TABLE 3

Systemic Symptoms in 34 Cases of Amebiasis

Symptoms	No. of Cases
Cardiac irregularity	8
Lassitude	10
Vertigo	10
Headache	4
Dyspnea	6
Weakness	9
Chest pain	4
Loss of weight	5
Paresthesias	5
Urticaria, severe	2
Fever	4
Arthralgias	5
Myalgias	4
Cough	3

TABLE 4

Prior Diagnosis in 34 Cases of Amebiasis

Diagnosis	No. of Cases
Spastic colon	10
Cholecystitis	6
Nervous indigestion	12
Chronic appendicitis	6
Neurasthenia	8
Labyrinthitis	7
Pruritis ani	10
Mucous colitis	13
Senility	6
Residual effect of CVA	6

Previous diagnoses

Antecedent diagnoses are summarized in Table 4. Mucous colitis was the most frequent (13 cases). Twelve patients were thought to have nervous indigestion, and 8 neurasthenia. A diagnosis of spastic colon had been made in 10 cases. Chronic cholecystitis was diagnosed in 6, but cholecystograms revealed typical changes in only 1. Six patients had been advised to have an appendectomy, but symptoms subsided following disappearance of amebiasis. Seven patients had been successfully treated for labyrinthitis, and 10 for pruritis ani. In 6 cases the gastro-intestinal symptoms that were thought to be the effects of senility and cerebrovascular accidents subsided after treatment with anti-amebic drugs.

Complications

In Table 5 the complications present in the 34 cases of amebiasis are listed. Anal fissure was found in 9, perirectal abscess in 2, chronic cholecystitis in 1,

TABLE 5

Complications in 34 Cases of Amebiasis

Complication	No. of Cases
Secondary anemia	6
Diverticulitis of colon	3
Pleuropulmonary amebiasis	2
Chronic cholecystitis	1
Anal fissure	9
Pylorospasm	6
Amebic hepatitis	8
Perirectal abscess	2

TABLE 6

Number of Courses of Drug Required for Cure in 34 cases of Amebiasis

Drug	Number of Cases Treated by Each Course of the Drug			
	Course 1	Course 2	Course 3	Course 4
Milibis with Aralen	18	14	3	1
Carbarsone	3	2	1	—
Diodoquin	13	9	2	2

diverticulitis of the colon in 3, and pylorospasm in 6. Secondary anemia was not common, being present in only 6 cases or 17.6 per cent. Amebic hepatitis was a complication in 8 cases (24.7 per cent). Among the 8 patients with amebic hepatitis, there were 2 with pleuropulmonary amebiasis; such cases constitute diagnostic problems in pulmonary pathology of unknown etiology (2).

Hematologic findings

There are no consistent hematologic findings in amebiasis. Leukocytosis was present only in the cases with hepatic and pulmonary complications. Eosinophilia was not consistent.

Methods

Adequate laboratory equipment and personnel are always necessary for the diagnosis of amebiasis (3). The identification of *Endamoeba histolytica* in a stool specimen constitutes the primary means of diagnosis. It is customary to ask the diarrheic patient to visit the laboratory for evacuation; then slides of the fresh feces mixed with saline are examined immediately. When diarrhea is not present, a saline purge is advocated. Oil, bismuth, magnesia, and barium will prevent proper examination of the stools. A high tepid saline enema may at times be adequate. Proctoscopic smears may occasionally be helpful. Serial specimens of feces are often necessary. For microscopic slides, in addition to saline suspensions, the "MIF" fixative of Sapero and Lawless (4) was used routinely. Iron hematoxylin stain was used for permanent fixation. The cysts of *Endamoeba histolytica*

may be isolated by the zinc sulfate centrifugal flotation technic of Faust *et al.* (5). Culture methods are seldom satisfactory. The complement fixation immunologic method may be useful for diagnosis when the amebae have invaded the tissues.

TREATMENT

There is no general agreement among parasitologists as to the most effective amebicide. Table 6 shows the results of treatment with 3 drugs and the number of courses required for cure.

The drugs used were: a combination of glycobiarsol (Milibis) with chloroquine (Aralen) in 18 cases; diiodohydroxyquin (Diodoquin) in 13 cases; and carbarsone in 3 cases.

The criteria for cure were negative findings in serial stool specimens, and asymptomatic progress for one year following completion of anti-amebic therapy.

SUMMARY

Thirty-four white geriatric patients with clinical amebiasis were studied with respect to gastro-intestinal and systemic symptoms, previous diagnoses, complications, and treatment. Laboratory diagnostic methods are outlined.

The pitfalls in differential diagnosis in the aged are stressed.

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IPRONIAZID IN THE TREATMENT OF RESISTANT HYPERTENSION.
A Preliminary Report on Twenty Intractable Cases

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Iproniazid has been found efficacious as a stimulant in the treatment of various forms of mental disease, primarily of a depressive nature (1, 2), and in a variety of other conditions (3–8). Another action of iproniazid is reduction in blood pressure; this effect is more marked at high dosage levels and occurs even in normotensive patients (9). Nussbaum *et al.* (10) reported that in 16 severely hypertensive patients treated with iproniazid for a two-month period, the blood pressure was lowered and there was marked subjective improvement. In a similar study Harnes (11) found that the hypotensive effect of iproniazid occurred mainly when the patient was in the standing position, although in one-third of his cases the decrease in blood pressure occurred with the subject in the supine position. Since these reports comprise a comparatively small and unselected group of patients, it was thought advisable to initiate a further investigation of the merits of iproniazid in this field. In addition, the incidence of toxic reactions with the higher dosages was observed.

CLINICAL MATERIAL AND METHODS

Patients

The study included 20 carefully selected hypertensive patients who had failed to respond to treatment with a variety of hypotensive agents, used alone and in combination (Table 1). With 1 exception, these patients had been under the author's care and observation during a minimal period of five years.

As is seen in Table 2, the group consisted of 13 women and 7 men whose ages ranged from 42 to 78 years (average, 59 years). Despite the previous forms of treatment (Table 1) the blood pressure remained persistently at levels of over 200/100 mm. Hg. In addition, all patients manifested electrocardiographic changes commonly associated with hypertensive heart disease, and all had hypertensive retinopathy. In 50 per cent of the cases, the retinopathy was of Grades III and IV according to the classification of Keith, Wagener and Barker.

Methods

The patients were told that a careful evaluation of their clinical state was to be made, necessitating certain physical examinations as well as laboratory tests. In order to establish a base line, all patients, after discontinuance of the previous hypotensive medications, were observed under the same regimen for a one-month period. This regimen consisted of a low-salt diet, and administration of 4 mg. of alseroxylon (Rauwiloid) each evening and 1.0 Gm. of chlorothiazide (Diuril) each morning. During this control period, blood pressure readings were taken twice weekly and the average of these readings represented the base level (Table 2).

At the end of one month, symptoms were noted, and a series of routine blood and urine

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TABLE 1

Hypotensive Agents Previously Used in Treatment of 20 Cases of Hypertension

	Hypotensive Drug	Daily Oral Dose (single or divided) (mg.)
Rauwolfia	Rauwolfia serpentina (whole root)	100.0–400.0
	Alseroxylon fraction (Rauwiloid)	1.0–8.0
	Single alkaloid (Reserpine)	0.1–0.8
Veratrum	Ester alkaloids of V. viride (Veriloid)	2.0–5.0 q.i.d.
	Purified alkaloids of V. viride	2.0–5.0 q.i.d.
	Protoveratrines A & B (single ester alkaloids of V. alba) (Veralba and Provell maleate)	0.2–0.5 q.i.d.
Ganglionic blocking agents	Hexamethonium chloride (Methium, Hexameton)	125.0–1500.0
	Pentolinium tartrate (Ansolysen)	20.0–500.0
	Chlorisondamine chloride (Ecolid)	12.5–200.0
	Mecamylamine hydrochloride (Inversine)	2.5–30.0
Hydralazine (Apresoline)		50.0–800.0
Chlorothiazide (Diuril)		500.0–1500.0

tests were performed. A chest roentgenogram and an electrocardiogram were obtained, a Master exercise test was made, and the eye grounds were examined. When indicated, excretion urography, a Regitine test, and determination of urinary catecholamines were carried out. Cardiac and renal functions were adequate in all but 1 patient who had previously suffered a right renal artery thrombosis. Mentation seemed unimpaired.

At this point, treatment with iproniazid (Marsilid, Roche) was initiated, while Rauwiloid and Diuril were continued. In order to obviate the psychologic effect so often associated with the institution of a new drug, the patients were not told that the new medication was a hypotensive agent. They were informed that we were interested in the effects on the psyche. The first patient received 50 mg. of iproniazid twice daily. Since this dose produced a marked fall in blood pressure accompanied by weakness and fatigue, all other patients were given initially 12.5 mg. daily; this amount was gradually increased every third day by varying increments dependent upon the blood pressure findings. The maximal dose used was 50 mg. three times daily. In general, the dosage was so adjusted that the patients could function normally and in comfort, and did not experience a reduction of blood pressure in the standing position which would result in weakness or syncope. Medication was continued until a fairly stable blood pressure level approximating 150/90 mm. was reached. The time required to achieve this level was extremely variable from patient to patient, as was the dosage required for maintaining it.

Blood pressure readings and urine studies were made twice weekly throughout the initial period until the blood pressure was stabilized; thereafter, once every two weeks. The blood pressure was obtained on each arm by palpatory and auscultatory methods, with the patient in the sitting position; this procedure was repeated after a five-minute interval and again at the end of the examination. One reading was taken with the patient in the erect position, to detect a possible orthostatic effect. The average of these readings was recorded.

Hemograms and bilirubin determinations were repeated every four weeks. Cardiac and renal surveys together with other general laboratory, roentgenologic or physical examinations were performed whenever indicated. In follow-up studies at six months and again at

TABLE 2

Effects of Iproniazid (Maximal Dose, 150 mg. Daily) on Blood Pressure and Blood Urea Level in 20 Hypertensive Patients

Patient No.	Age & Sex	Blood Urea Level (mg./100 ml.)			Average Blood Pressure (mm. Hg)		Alteration in Blood Pressure after 2 Wks.		Average Blood Pressure (mm. Hg)		Side-effects
		Before Therapy	After 5 Mos. of Therapy	After 1 Yr. of Therapy	Control Period	After 2 Wks. of Therapy	Systolic	Diastolic	After 6 Mos. of Therapy	After 1 Yr. of Therapy	
1	53F	24	16	14	220/118	158/88	−62	−30	152/80	138/76	Weakness and fatigue; dosage adjusted to 75 mg. daily.
2	47F	20	14	12	212/110	152/90	−60	−20	140/82	142/70	
3	60F	27	18	16	206/116	160/86	−46	−30	150/80	140/76	
4	55F	56	30	20	240/130	170/88	−70	−42	152/76	146/72	Orthostatic episode; dosage adjusted to 100 mg. daily.
5	68F	30	16	16	230/116	156/84	−74	−32	142/78	130/70	
6	66F	18	12	14	206/106	148/80	−58	−26	146/74	136/72	Blood pressure rose to 178/80 when Rauwiloid was discontinued.
7	61F	28	14	16	236/112	160/84	−76	−28	156/78	146/70	
8	42M	58	28	18	260/140	156/80	−104	−60	144/80	142/80	Orthostatic episode; dosage slowly adjusted.
9	71F	32	16	12	204/106	140/78	−64	−28	142/70	146/74	
10	72F	38	14	14	234/128	206/102	−94	−44	190/90	182/80	
11	66F	16	13	12	202/100	150/76	−52	−24	142/70	140/70	
12	76F	18	16	10	214/108	150/90	−64	−18	146/84	136/76	
13	78F	22	12	12	236/110	160/88	−76	−22	154/80	142/74	
14	56M	14	14	14	210/102	140/70	−70	−32	146/78	140/76	
15	60F	30	18	16	256/124	190/90	−66	−34	168/90	156/86	Faintness and weakness; dose adjusted to 125 mg. daily.
16	52M	20	12	12	218/106	150/76	−68	−30	146/70	140/70	
17	48M	16	14	11	208/106	136/70	−72	−36	140/70	136/68	
18	52M	18	16	14	218/102	146/76	−72	−26	142/72	138/70	
19	56M	16	12	12	206/104	150/88	−56	−16	148/78	140/76	
20	64M	28	18	15	256/124	182/94	−74	−30	170/90	162/84	
Average	59	26.6	16.2	14.0	227/114	158/84	−69	−30	151/78	144/75	

one year, the patients were once more evaluated; the blood pressure readings were taken and the patients were examined for signs indicating side-effects.

RESULTS

In 13 patients, the blood pressure began to drop gradually seventy-two hours after the initiation of iproniazid (Marsilid) therapy. After that time, with increasing doses given over periods of varied length, it was possible to maintain the blood pressure in these 13 patients at or near accepted normotensive levels, *i.e.*, 150/90 mm. Hg or below. In 6 other patients, although the pressure did not return to normal, it was stabilized at a fairly satisfactory level. One patient showed only a minimal response; nevertheless, the blood pressure level was considerably lower than that prior to the initiation of iproniazid therapy. Results of therapy are summarized in Table 2.

As shown in Table 2, the blood pressures during the control period ranged from 202/100 to 300/146, with an average of 227/114 for the 20 patients. After six months of treatment the range was from 140/70 to 190/90 with an average of 151/78. The average drop after two weeks of therapy was 69 mm. Hg (systolic) and 30 mm. (diastolic). As may also be seen in Table 2, the average concentration of blood urea fell from the control level of 26.6 mg., to 16.2 mg per 100 ml. after five months of therapy. At the end of one year, the blood pressure drop had been maintained and in some cases was lower than at six months. This was also true for the blood urea levels.

Retinopathy, heart size, electrocardiograms and renal function showed improvement in all but 1 patient. In the 10 patients who originally had Grade III or IV patterns of retinopathy, the pattern was Grade II after treatment.

An additional striking feature was the subjective and objective improvement in patients with cardiac decompensation. Heart size decreased, and the electrocardiographic record of left ventricular hypertrophy showed improvement. Frequently digitalis could be discontinued. Relief of any coexistent angina, was also noted. No less impressive was the psychologic improvement in all the patients, many of whom remarked that they had not felt as well in years. This sense of well-being had not been noted with any of the potent antihypertensive medications previously used. A few of the patients with a poor appetite began to eat and put on weight.

No two cases required the same dosage or showed a similar pattern of response. The following cases illustrate the extremes in the responses:

Case 4

M. R., a 55-year-old white female first learned of her hypertension following an attack of rheumatoid arthritis in 1951. Except for this episode and a diagnosis of multiple fibroids of the uterus in 1940, her history was not significant. Familial history revealed that her mother died of a "stroke" at the age of 56 "due to high blood pressure," and that her father died at the age of 58 following a myocardial infarction. In 1951, when the patient had been hospitalized for rheumatoid arthritis, hypertension had been noted, with a blood pressure in excess of 200/100 mm. Hg. In 1953, when she was first seen by the author, she complained of severe headache, exertional dyspnea and precordial discomfort. Her blood pressure at that

Average	59	26.6	16.2	14.0	227/114	158/84	−69	−30	151/78	144/75

time was 260/130. Physical examination disclosed the following significant findings: The eyegrounds exhibited Grade III hypertensive retinopathy. A Grade III apical systolic murmur was heard at the apex of the heart and was transmitted to the axilla and the base; the aortic second sound was accentuated and tambour-like. There was no edema or cyanosis, but scattered moist rales could be heard at the bases posteriorly. Urinalysis showed 2-plus albumin and numerous renal casts. The specific gravity of the urine was 1.014 and 1.018 after the concentration test. The blood urea nitrogen level was 56 mg. per 100 ml. The erythrocyte sedimentation rate was 32 mm. per hour. The red and white blood cell counts, differential count and hemoglobin level were not remarkable. Results of the Wassermann were negative. The electrocardiogram demonstrated no abnormality but was of a hypertensive pattern. A chest roentgenogram indicated enlargement of the heart to the left and downwards, and a tortuous aorta. The fasting blood sugar level was 123 mg. per 100 ml., and after a 2-hour glucose loading test 130 mg. per 100 ml.

The patient was digitalized and given 2 ml. of mercaptomerin (Thiomerin) daily.

A low-cholesterol, low-salt regimen was prescribed, along with a reserpine-hydralazine combination (0.2 mg. of Serpasil and 50 mg. of Apresoline per tablet) three times daily. She was seen weekly for the first month and, during that period, the blood pressure fell to 240/130, fluctuating at this level for two months. For a period of four years, the patient was given in succession rauwolfia, mercaptomerin, Peritrate, phenobarbital and Ansolysen, Mio-Pressin, Hydergine and Inversine, without any significant effect on the blood pressure.

Iproniazid therapy was then instituted, according to our routine regimen. The base level of blood pressure as defined herein was 240/130 mm. Hg. The dosage schedule of the drug was as follows: (For the sake of comparison the blood pressure readings are also noted.)

Date	Daily Dose of Iproniazid (mg.)	Blood Presssure (mm. Hg)
1957		
Nov. 2	12.5	240/130
Nov. 6	25.0	190/98
Nov. 10	37.5	180/90
Nov. 12	25.0	122/70
Nov. 16	31.25	170/88
Nov. 20	31.25	164/80
Nov. 24	31.25	168/82
Nov. 28	31.25	166/84
Dec. 3	37.5	170/86
Dec. 7	37.5	160/80
Dec. 11	37.5	150/78
Dec. 15	37.5	152/76
Dec. 19	37.5	156/80
Dec. 23	37.5	160/84
Dec. 27	37.5	166/86
1958		
Jan. 2	50.0	170/88
Jan. 6	50.0	182/70
Jan. 10	50.0	148/72
Jan. 14	50.0	152/76

To date the blood pressure has been maintained at a level fluctuating between 136/70 and 172/88 with iproniazid therapy in a dosage of 50–100 mg. daily. The patient is happy with the results and is feeling well.

Case 10

F. B., a 72-year-old white female had a history of hypertension of approximately ten years' duration. There was nothing significant in the past history. When first seen by the author in February 1953, her blood pressure was 300+/146 mm. Hg. She complained of a severe pounding headache, dizziness, poor vision, a feeling of "sand in the eyes," breathlessness, two-pillow orthopnea, swelling of the legs and other symptoms of cardiac decompensation. The chest roentgenogram demonstrated an enlarged and dilated heart and changes in the lung consistent with hypertension and heart failure. Physical examination revealed enlargement of the heart to the left and downward, a heaving apical impulse, a Grade IV systolic apical murmur transmitted to the axilla, and a long, low-pitched diastolic murmur at the left sternal border from the base downward. There was Grade IV hypertensive retinopathy. Urinalysis showed 2-plus proteinuria, numerous casts and a specific gravity of 1.012 (1.016 after a concentration test). The blood urea nitrogen level was 38 mg. per 100 ml. The erythrocyte sedimentation rate was 48 mm. per hour. The erythrocyte count was 3,400,000 per cu. mm., and the hemoglobin level 11.2 Gm. per 100 ml. Results of the Wassermann test were negative. The level of fasting blood sugar was 132 mg. per 100 ml. An electrocardiogram showed numerous ventricular extrasystoles and a marked hypertensive pattern.

After nearly five years of treatment similar to that in Case 4, the stabilized control level of blood pressure was 234/128. Following the routine observation period and the regimen previously described for Case 4, iproniazid therapy was started in a dosage of 12.5 mg. daily, and this amount was increased at three-day intervals by 12.5-mg. increments. The blood pressure readings and daily doses of iproniazid were as follows:

Date	Daily Dose of Iproniazid (mg.)	Blood Pressure (mg. Hg)
1957		
Nov. 19	12.5	234/128
Nov. 23	25.0	218/118
Nov. 27	37.5	214/110
Dec. 2	50.0	206/102
Dec. 6	62.5	210/108
Dec. 10	75.0	206/104
Dec. 14	100.0	190/102
Dec. 18	112.5	186/98
Dec. 22	125.0	192/100
Dec. 27	137.5	196/104
1958		
Jan. 2	150.0	194/100
Jan. 6	150.0	204/102

Blood pressure readings were taken twice weekly for a month. At the time of this writing the pressure was fluctuating between 190/90 and 226/114 mm. Hg. The patient felt better with this medication than with any of the previous regimens. However, unlike the patient in Case 4, she could not be listed as showing a good response because the blood pressure continued at a level above 200/100 mm. Hg.

Side-effects. In 6 of the 20 patients, weakness, fatigue and dizziness preceded episodes of orthostatic hypotension; syncope occurred in 1. All the other 14 patients were free from side-effects. None showed any evidence of hepatitis, as reflected in results of the bilirubin test for liver function.

DISCUSSION

Adequate evaluation of the efficacy of any treatment will depend on how carefully the patients were examined prior to study. Insufficient data and too short a period of study can only lead to confusion regarding the results of any regimen. It is likewise important in the collection of data that there be close supervision and observation of the patients. For these reasons the group selected for the study was small and was comprised of patients whom the author had observed closely for the previous six years.

Until more is known about the pathogenesis of hypertension, the goal of therapy and the criterion of efficacy are judged by reduction in blood pressure to as near a normal level as is consistent with the comfort and well-being of the patient. In addition, the clinical signs are always indicative of improvement. Attendant upon the reduction of blood pressure, there is improvement in the funduscopic picture—hemorrhages and exudate disappear, and papilledema focal constrictions, arteriolar narrowing and arteriovenous constriction are greatly reduced. There is convincing evidence that hypertensive patients with renal impairment have a much better prognosis when the high blood pressure is effectively treated.

The effectiveness of iproniazid when used alone in the treatment of hypertension has been reported by others. In our study, its particular value lay in an adjuvant effect with other medications in cases of severe hypertension. Discontinuance of either the chlorothiazide or the reserpine preparation resulted in a rise in blood pressure, although never to the former high levels. Iproniazid seemed to neutralize the depressive effect of the rauwolfia derivatives.

The incidence of side-effects due to administration of iproniazid has been reported (12–15). In our patients there was ample time for modification of dosage between the premonitory symptoms of orthostatic hypotension and the actual syncope that occurred in 1 patient. Possible unfavorable reactions can be decreased to a minimum by cautiously increasing the dosage of iproniazid by 12.5-mg. increments every third day and by frequent observation of the blood pressure. The gain in weight may be undesirable in patients who are already overweight.

In rare cases, hepatotoxic effects have been reported (16–19). Although no hepatotoxic effects were noted in the follow-up period in our series, the possibility exists that the protracted medication required by hypertensive patients may entail some other risk, which only continued study can establish.

SUMMARY AND CONCLUSIONS

Twenty patients with a history of long-standing hypertension which had been refractory to all forms of treatment, including chlorothiazide, were studied. For a one-month observation period, each patient received a combination of a reserpine preparation and chlorothiazide, and the blood pressure remained at a level of about 200/100 mm. Hg. Then iproniazid was administered.

In 13 of the 20 patients there was a prompt response to iproniazid therapy,

with return of the blood pressure to approximately normotensive levels (150/90). In 1 patient the initial blood pressure was 300+/146, and could be reduced to only 192/92 following six months, and to 182/80 after one year of iproniazid therapy. In 6 patients, although not returning to normotensive values, the blood pressure became stabilized at a reduced level.

Retinopathy, heart size, electrocardiographic changes and renal function showed improvement in all but 1 patient. Fourteen patients were free from troublesome side-effects. Symptoms of weakness, fatigue and dizziness appeared in 6 patients, indicating that orthostatic hypotension was impending and that the dosage should be reduced immediately.

During iproniazid therapy all patients expressed a sense of psychologic well-being that they had not experienced with any other potent hypotensive medication.

In view of the brevity of the follow-up period (one year) the results should be interpreted with some reservation. Nevertheless it can be stated that, when used in conjunction with reserpine-chlorothiazide and a low-salt diet, iproniazid may be of distinct value in the treatment of hypertension provided the patients are regularly observed for the possible appearance of side-effects.

Iproniazid is one of the older monoamine oxidase inhibitors and has all but been abandoned in clinical medicine because of this serious side-effect and because some of the newer psychic energizers appear more promising. However, toxic effects on the liver were not observed in our small series.

Orthostatic hypotension can be a serious complication in older people. It is possible that some of the newer monoamine oxidase inhibitors do not have this effect and do not cause liver damage. A number of analogs of iproniazid, as well as other monoamine oxidase inhibitors, are presently available for clinical investigation. Results of the studies reported here indicate that the combination of a relatively nontoxic monoamine oxidase inhibitor with chlorothiazide and a low-salt diet would be worthy of intensive investigation.

Addendum

For the past year, additional studies have been made with the 20 patients mentioned in this paper, using monoamine oxidase inhibitor No. 516 (now available from Lakeside Laboratories as Catron). The biochemical effect of this drug is similar to that of other monoamine oxidase inhibitors, namely, reduction of the conversion of orally administered serotonin to 5-hydroxyindoleacetic acid (5-HIAA), the end-product of MAO activity on this amine (20, 21). After the blood pressure was lowered with the use of this preparation, a maintenance dosage of 12 to 21 mg. daily was adequate. In this added investigation, No. 516 (phenylisopropyl hydrazine) was substituted for iproniazid and used under the same conditions. Daily doses of 12 to 50 mg. were given according to graduated schedules, as prescribed for iproniazid. The therapeutic results paralleled those obtained with iproniazid.

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NUTRITION AND THE GERIATRIC PATIENT*

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Who are the elderly? In what age bracket are they included? Webster defines the elderly as past middle age. Nutritionists, in studying the needs of the geriatric patient, consider not only the chronologic age but also the mental, emotional and physical ability.

The role of nutrition in geriatrics is to conserve health and to equip the elderly to withstand the onset of chronic degenerative diseases such as chronic heart disease, cancer, hardening of the arteries, cerebral hemorrhage, kidney disease, and arthritis.

Malnutrition is the precursor of many dietary problems involving this group. In considering these problems we study both the scientific role of food in relation to body needs and also the psychologic aspects.

Body weight

Either overweight or underweight may result from malnutrition. Some specific causes of underweight are: poor appetite, impaired digestion, poor absorption, lowered gastric acidity, inadequate food intake, and poor choice of foods.

Energy requirements decline progressively after early adulthood because of a decrease in the basal metabolic rate as well as lessened physical activity. However, the appetite of the elderly person does not always decrease with this decline of energy requirements. Moreover, loss of teeth and the dulling of taste may lead to an individual preference for soft bland food of high caloric content, thus increasing the body weight.

The single most important factor in the treatment of obesity is a decrease of caloric intake. At the same time, the food eaten should carry the essential elements, *i.e.*, proteins, minerals and vitamins.

Protein and vitamins

The educational status of the old person often results in lack of knowledge pertaining to the types of protein food, the efficient use of cooking facilities, and the importance of teeth for the proper digestion of meats and other foods.

Several deficiencies can be cited as a result of an inadequate protein intake, such as edema, itching of the skin, chronic eczema, fatigue, tissue atrophy, slow healing of wounds, and lowered body resistance.

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Calcium and vitamin C are often lacking in the geriatric diet, due to the lack of milk and citrus fruits. Leg cramps during sleep may be associated with deficient calcium intake, and internal hemorrhages can result from insufficient vitamin C.

Psychologic aspects

Since each elderly person has dietary problems in relation to his mental, physical and emotional needs, there are almost as many dietary problems as there are elderly people.

We can classify dietary problems on a scientific basis and utilize a master plan in solving some of them.

In some old people there is a slackening of function in the digestive system. A clear soup at the beginning of a hearty meal may stimulate the gastric secretion. Four to five small meals per day may be digested more easily than three larger meals. Sleep-inducing relaxation often follows the drinking of a hot nourishing beverage.

Psychologically each old person's problem needs special recognition. In preparing food for people who have poor teeth or no dentures, it is necessary to think of what effect the use of ground, pureed and strained foods has on emotional status. Is it reclassing the old person as an infant? Will the consistency of the food prevent stimulation of the appetite, because of the lack of variety and color? Has independence been usurped by not allowing the patient to feed himself, to select foods, or to request a specific dish?

Habit is culture—developed with the individual. After 60 or 70 years of habit development, radical changes are not welcomed. We seldom find people past the age of 60 who are interested in learning new facts about nutrition; any necessary changes, nutrition-wise, require tolerance and patience. The same consideration can be applied to superstitions and fallacies regarding food—"The known is familiar; the unknown is mysterious." In either area a kind friendly atmosphere with a homelike environment slowly eliminates these unhealthy situations. Serving meals family style in a well ventilated and decorated dining room (preferably at small family-size tables) favors the development of this needed atmosphere. Dietary personnel need to be impressed with the fact that eating is a slow process with the elderly, and consideration has to be given the slow eater. Patients physically unable to eat in the dining area should have their food served on a tray in a room other than their sleeping room, and be permitted to have companions during meal time.

When we stop learning and being interested, we begin to grow old. There is no physiologic age at which we must stop accustomed activity; hence, there is no age at which we must be labeled "old"—provided we continue to be interested, use our bodies, and eat well-balanced meals.

Community services

Community-wise, we are obligated to keep our aged people independent and interested in life. In view of the emphasis recently placed on the needs of the

aging, it is necessary to explore ways of meeting the nutritional problems for this large segment of the population.

The changing older population picture indicates that more consideration must be given to the elderly person in the home, as well as in institutions. Proper nutrition of the aged in either setting presents a special set of problems—the planning, purchasing, preparation and expense of food. For the person living alone and for the operators of a group-feeding arrangement, this is no easy task —if not a forgotten one!

Here success of any kind requires community organization of those services which provide the elderly with the type of assistance needed. In the field of nutrition the sharing of knowledge and responsibility with other specialists involved in services to this group should be emphasized. At present, community resources offer nutrition assistance in several ways:

Educational—Materials, consultation, workshops and institutes for professional personnel, operators and owners of Nursing Homes and Homes for the Aged. Most health and welfare agencies and educational institutions provide educational materials and services of one type or another.

Financial—Assistance from welfare and social agencies granting funds for the purchase of food.

Physical—Assistance in planning, purchasing, preparing and serving food, *i.e.*, projects such as "Meals on Wheels."

The "Meals on Wheels" project provides for a hot meal and a snack to be delivered daily to the old person in the home. A daily fee, dependent upon the financial status of the recipient, is charged. The economic factor does not always involve the mere granting of money; often the problem lies in lack of equipment for preparation and storage, lack of means for shopping, or lack of knowledge about how to buy with a limited income.

Old persons may be referred for this assistance from various sources such as private physicians, hospitals, agencies or individuals. The cost of home care versus general hospital care has to be considered.

Services should be limited only by the numbers that can be served efficiently and by the complexity of the requirements. Special diets, served upon written order of the physician, can be easily arranged by modifying the regular menu. At present, special diets are restricted to a comparatively small number of persons. Very few institutionalized programs are designed for feeding the elderly. Assistance is needed in planning, preparing, and storing food, buying and proper care of equipment, appreciation of food patterns and habits, and provision of special diets.

The following questions seem pertinent: What kind of assistance can be provided in your community? How can available services be used to supplement or complement each other? What is a practical feasible means of meeting the nutritional needs of the aged? Would a community kitchen or restaurant where the elderly may purchase meals be useful? Would a food commissary, hospital, or agency providing food service and delivery to private homes and institutions be beneficial?

Programs for meeting the nutritional needs and problems of the elderly might be improved and promoted if we were to answer some of these questions.

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REHABILITATING THE MOST SUPERANNUATED AND LONGEST HOSPITALIZED PSYCHOTIC PATIENTS*

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Rehabilitation of the elderly chronically psychotic patient is one of the most neglected aspects of our mental hospitals today. The reasons for this neglect are manifold and no doubt involve both realistic and unrealistic motivation. Although unfortunate, it is not difficult to understand why a patient who is physically debilitated, intellectually deteriorated, emotionally disturbed and socially and economically destitute, is shunned by professional workers with much the same reaction as that of relatives and friends, and is regarded as a hopeless case. Nor can one discount our past inability to do anything of appreciable significance about most of the mental ills of the aged. This factor in itself led to professional pessimism which has been carried over to the present time. To be considered also, are the more subtle influences such as the negative attitude in our society toward the elderly in general, and our inherent fear of growing old.

In many cases, however, our pessimism is unjustifiable. With the exception of the severe dementias, it has been shown that most of the psychoses of later maturity and even of the advanced senium are susceptible to at least symptomatic improvement (1–6). It is the purpose of this article to demonstrate that with therapeutic management, careful planning, and interdisciplinary cooperation and effort, it is possible to rehabilitate and restore to the community even those elderly patients with the longest established psychoses, initially regarded as requiring permanent institutional care. These patients are typical of the geriatric population in our mental hospitals and present a variety of physical, emotional and social problems. Due to space limitations, the case histories are presented here in condensed form.

CASE REPORTS

Case 1

J. Z., a 63-year-old white unmarried veteran, was admitted in September 1947, after having been hospitalized almost continuously since his discharge from the service in 1919. Approximately one month after discharge from the service he had become psychotic and required hospitalization. The diagnosis of dementia praecox, hebephrenic type, was established at that time. He was given custodial care and transferred to another institution in 1937. He was then given routine hospital care and symptomatic medication which had little, if any, effect on the psychotic symptoms. The prognosis was considered poor, continued hospitalization was recommended, and in 1947 the patient was transferred to this facility.

Shortly after his arrival he was granted open ward privileges and assigned to physical

* The data for this paper were collected at the Veterans Administration Hospital, Tomah, Wisconsin with which both authors were formerly associated. The opinions expressed are not necessarily those of the Veterans Administration.

and occupational therapy. He was also exposed to the patients' self-government and corrective therapy programs[1] (7, 8). His self-care habits began to improve markedly and he cooperated with the personnel to a greater extent. Psychologic tests given on August 24, 1953, revealed the presence of a chronic schizophrenic reaction without, however, the disorganization and acute symptoms usually found in a hebephrenic condition. Clinically the patient appeared to be relatively integrated and less indifferent to his surroundings. He continued to manifest some apathy but no primary schizophrenic symptoms were apparent. In the opinion of the staff he was in a state of partial remission. Since the patient had but one living relative (a brother who was either unwilling or unable to take custody of the patient), a foster-home program[2] was recommended. The patient, however, at this point was naturally fearful about leaving the hospital. At first he rejected the plan, but after numerous discussions over a period of several months and visits to prospective homes with the social worker, he gradually changed his attitude and became more receptive to the idea. He was assured that he would be able to continue his occupational projects in the home, and the occupational therapist had been alerted to this. She worked closely with the patient on his projects, told him how and where he could obtain supplies, and reassured him that he was capable of working independently. He was finally placed in a home at his request. Two years later he was continuing to make a very satisfactory adjustment.

Case 2

T. J., a 61-year-old white unmarried veteran, was admitted on April 12, 1948, by transfer after having been hospitalized continuously since 1931. Following his discharge from the service in 1919 he manifested confusion, memory impairment, and became threatening and assaultive. He was committed on April 19, 1924, actively hallucinated, slightly depressed, and revealing poor insight and judgment. Psychometric examination given at that time revealed the presence of a psychotic reaction. The patient escaped in August 1924, and remained out of hospitals until February 1931. At that time he was readmitted in an acute psychotic state. He was transferred from hospital to hospital and received largely custodial care. During the course of these hospitalizations he became manneristic, negativistic, and severely withdrawn. The prognosis had thus been considered poor and continued hospitalization recommended.

On admission to this hospital the patient was given open ward privileges and assigned to ward housekeeping duties through the patients' self-government program. He became more cooperative, and with the help of the psychiatric aides his work capacity improved. Subsequently he was assigned to corrective therapy on the ward and group psychotherapy. These therapies appeared to stimulate the patient to better communication of his thoughts and feelings and more socialization with others. He became more relevant and coherent, and his mood more pleasant. The degree of remission seemed sufficient to justify a trial

[1] These have been described in previous publications (7, 8). The self-government program is a formally structured, group-centered discussion program which is regulated and maintained by the patients. Its basic purpose is to restore feelings of personal adequacy, encourage active participation in the events of daily life, and develop the patient's interest in persons and things outside of himself. The corrective therapy program is a group-centered technique designed to motivate withdrawn patients and improve their physical well-being and morale through group-action methods.

[2] This program was designed to provide suitable homes for patients who had responded to treatment and training to such an extent that it was believed they could adjust to living under close supervision in a home, and profit from the individual attention which comes with family life. The program was continuously geared to meet individual needs. Several planning sessions were held with the patient prior to his placement, and he was closely followed after his placement through frequent follow-up interviews. Since most patients either had no relatives or were rejected by them, this program was an indispensable part of the total rehabilitation effort.

visit. Since there were no relatives willing or able to take the patient out of the hospital, the social worker was called upon to secure a foster home. The patient, having become well institutionalized, at first rejected the plan. He was seen by the social worker in group meetings for a period of eight weeks, made numerous visits to the prospective home, and was finally motivated toward accepting the placement. He was placed in the home at his request and nineteen months later was continuing to make a very satisfactory adjustment.

Case 3

H. D., a 67-year-old white unmarried veteran, was admitted in June 1947, by transfer. He had been hospitalized almost continuously since his discharge from the service in 1918 and his case had been diagnosed as dementia praecox, catatonic type. The symptomatic manifestations of the illness at that time were multiple, involving blatant auditory hallucinations, confusion, marked indifference to his surroundings, and mutism. He had to be tube-fed and was almost totally inaccessible. He was given routine hospital care and symptomatic medication throughout the course of his hospitalization, without any appreciable change in his behavior. The prognosis was considered poor, and continued hospitalization recommended.

On admission here the patient was examined and the diagnosis of schizophrenic reaction, catatonic type, continued. The acute symptoms previously observed, however, were not in evidence at the time of admission. Instead, the patient appeared seclusive, dull, and apathetic. He was assigned to occupational therapy and ward housekeeping duties through the patients' self-government program. Under this regimen he showed very slow, but consistent, improvement. In 1954, recovery was sufficient to permit partial open ward privileges and freedom of the hospital grounds. In 1956 he was granted full open ward privileges. At this time he appeared to be in a fair state of remission, the only recognizable psychiatric symptoms being a tendency to withdraw from others. He was well oriented, his conversation was rational, and his self-care habits were adequate. At this time he was also making an excellent adjustment in the occupational therapy clinic. He was actively engaged in weaving and he cooperated in group projects which involved other elderly psychotic patients. In January 1958, he had recovered sufficiently to be considered for a trial visit. Since there was no known living relative willing or able to take custody, a foster home was secured and the patient was placed there at his request on October 23, 1958. He has adapted successfully and continues to remain happy and well adjusted.

Case 4

A. W., a 64-year-old white unmarried veteran, was admitted in August 1952. He had been hospitalized for the previous twelve years and was well institutionalized when admitted to this facility. His mental symptoms dated back to 1928, at which time he was displaying definite paranoid trends with ideas of reference and persecution while also drinking to excess. However, he did not require hospitalization at that time. In 1940 he began to hear voices while he was working at a CCC camp. These voices threatened his life and accused him of masturbating and molesting little girls. They were quite accusatory, and finally the patient became so reactive concerning them that he slashed his wrists and throat in an attempt to commit suicide. He was hospitalized in 1940 and transferred to several different hospitals over the years, receiving routine but ineffectual care. The diagnosis throughout the course of these hospitalizations was dementia praecox, paranoid type. The prognosis was considered poor and continued hospitalization recommended.

On admission to this facility the patient was examined, and the diagnosis of schizophrenic reaction, paranoid type, was continued. In the opinion of the staff he was not a suicidal risk and was therefore granted open ward privileges. He was also given an industrial therapy assignment as a kitchen helper, was assigned to group psychotherapy, and actively participated in recreational and patient government affairs. Under this regimen, he showed dramatic improvement. He became more rational and coherent within his environment. His hallucinations and paranoid delusions eventually disappeared. He cooperated with

ward personnel to the fullest extent and became quite congenial in his associations with them as well as with other patients. In fact, the only recognizable psychiatric symptoms at the time of the trial visit were some benign defects of judgment and emotional dullness. In view of the patient's consistent and favorable improvement, the staff voted for trial visit disposition with foster home care. Through group discussions and repeated visits to the foster home, the patient was motivated to accept the placement. He was placed in the home in April 1958, and continues to be happy and well adjusted.

Case 5

H. G., a 64-year-old unmarried veteran, was admitted in June 1958, by transfer, having been hospitalized continuously since 1934. His mental symptoms, however, dated back to 1918 while he was in military service. In 1926, ideas of reference developed, as well as abnormal fears and delusions of a religious nature. In 1934 his condition became acute, necessitating hospitalization. He continued to have many abnormal fears and poorly systematized delusions of persecution. In 1935 he became self-assaultive and made a feeble attempt to commit suicide. Following a period of study, a diagnosis of dementia praecox, catatonic type, was made. During these hospitalizations his behavior fluctuated between periods of hyperactivity which usually required restraint and sedation, and periods of extreme withdrawal and mutism. Throughout the years his prognosis was considered poor and continued hospitalization was recommended.

On admission to this facility, the patient was examined and the diagnosis of schizophrenic reaction, catatonic type, was continued. The psychosis, however, appeared to have leveled off from that which had been previously described. Although the patient manifested symptoms of chronic institutionalization such as apathy, withdrawal and indifference toward the environment, he did not display any of the previously described hallucinations, delusions or hyperactive behavior. The psychosis was therefore considered to be in partial remission. A treatment regimen was started, with recommendations for a trial visit in the near future. Accordingly, the patient was granted open ward privileges, and assigned to occupational therapy and group psychotherapy; he was given a ward housekeeping assignment and he took an active part in the geriatric club committee of the patient government organization. He was also given 100 mg. of chlorpromazine (Thorazine) three times daily. In occupational therapy the patient was interested in weaving rugs and became rather proficient at it. He performed his other assignments faithfully, cooperated with everyone to the fullest extent, and became more responsive to his environment. None of the symptoms previously recorded was manifest. Explorations by the social service department revealed that the patient's relatives were unwilling to accept him, regardless of his progressive improvement. It was the opinion of the staff that the patient was no longer in need of hospitalization. Thus it became necessary to secure a foster home for him. This was accomplished, and the patient pleasurably accepted the placement. He was placed in the home on August 10, 1958, and continues to be happy and well adjusted.

COMMENT

Five cases have been presented here for illustrative purposes only. A much larger number of patients with the same problems have been treated in a similar manner, with similar results. Many of them have been returned to the community. Others, unfortunately, have had no pension or income to meet expenses and often have had to remain in the hospital for this reason alone. A few have found security in the hospital and prefer to remain in such a relative sanctuary. The results obtained with these patients exemplify how chronic elderly psychotic patients can be helped significantly with comprehensive medical management and psychiatric treatment. The popular notions of the hopelessness and irre-

versibility of such psychopathologic conditions among elderly persons are untenable in a large proportion of cases.

The possibility of successful treatment is demonstrated by the fact that we were able to dehospitalize 5 patients whose rehabilitation had previously been regarded as hopeless—2 after twenty-seven years of hospitalization; 1 after thirty years; and 2 after twenty years.

During the past year 4 additional patients have been dehospitalized. These were from the most superannuated groups in four wards of a building housing 164 geriatric patients regarded as hopelessly refractory to the influence of combined disciplines.

These results highlight the outmoded perspective which is unjustifiably operative in too many such cases.

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DIABETES MELLITUS, IDIOPATHIC MYOCARDIAL HYPERTROPHY AND PAROXYSMAL ATRIAL FLUTTER

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In a large number of diabetics, particularly those past middle age with diabetes in mild form, coronary heart disease eventually develops. Treatment with insulin or oral hypoglycemic agents permits these patients to live long enough to show atherosclerotic vascular changes. In general, elderly diabetics maintained by diet only, or persons who may not even know they are diabetic, are the ones in whom anginal symptoms suddenly appear.

This report concerns an unusual case of the sudden development of atrial flutter in a previously healthy person who later was found to have diabetes mellitus and possible idiopathic myocardial hypertrophy.

CASE REPORT

M. Y., a 65-year-old obese white housewife, was admitted to the hospital complaining of anginal pain radiating to the left arm for the first time. Two hours previously she had received injections of morphine and atropine. She was in a semistuporous condition, and there was no apparent relief of the precordial distress. Hypoxia and cyanosis were quite evident, so she was placed in an oxygen tent. It was soon discovered that the semistuporous condition thought to be the effect of morphia was due to diabetic acidosis, and that the patient was on the verge of coma.

Her blood pressure was 140/85 mm. Hg bilaterally. The heart sounds were irregular and of poor quality, but no murmurs were heard. There were a few scattered rales at the lung bases. Laboratory tests: The level of blood sugar was 460 mg. per 100 ml., serum nonprotein nitrogen 31 mg. per 100 ml., cholesterol 344 mg. per 100 ml., chlorides 93 mEq. per liter, and CO_2 combining power 16.9 mEq. per liter. The urine (specific gravity, 1030) was acid and contained a slight trace of albumin, a trace of sugar, and 4-plus acetone; the sediment contained 1–2 leukocytes and 8–10 epithelial cells per high-power field.

A chest roentgenogram (Fig. 1) revealed a prominent left ventricle, atherosclerosis of the aortic arch, and an increase in the cardio-thoracic ratio of 15.3 cm. to 25.5 cm.; it also showed increased congestion of the main pulmonary arteries as well as of the lesser ones at the base. After Dicumarol and insulin therapy had resulted in marked clinical improvement and lowering of the blood sugar level, a second chest roentgenogram (Fig. 2) showed a diminished cardio-thoracic ratio of 13.3 cm. to 27.2 cm. The congestion of the vessels had disappeared and the lung fields were well pneumotized.

The initial electrocardiographic tracing (Fig. 3) demonstrated atrial flutter and myocardial infarction with tall R waves in the V-leads 1, 2 and 3, which is a typical picture of right ventricular hypertrophy. Dicumarol, digitoxin and insulin were started. After the urine became sugar-free and the blood sugar level had decreased to 185 ml. per 100 ml., a second electrocardiographic tracing (Fig. 4) demonstrated a sinus rhythm replacing the atrial flutter, persistent Q waves in the V leads 1, 2 and 3, but no evidence of R waves in the same V leads. Six weeks later, when the patient was ambulatory, a tracing (Fig. 5), using the entire twelve leads on one side of a chart (1), demonstrated that the T waves in lead

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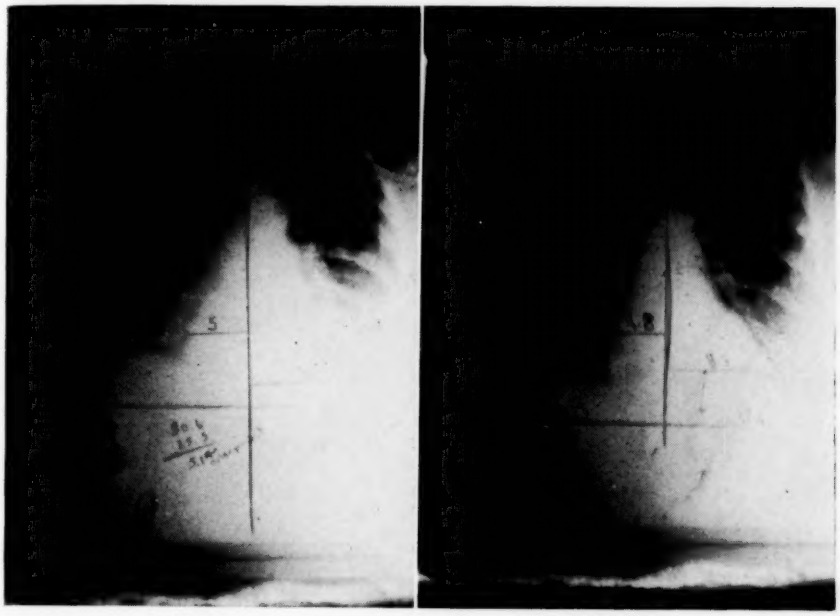

FIG. 1 FIG. 2

FIG. 1. Increase in cardio-thoracic ratio, prominent left ventricle, and increased congestion of main pulmonary arteries as well as of the lesser ones at the base.

FIG. 2. Diminished cardio-thoracic ratio after treatment. Congestion of the vessels has disappeared.

1 were now upright; the heart was in a horizontal position; there was counter-clockwise rotation into V_2, and T-wave inversion in all the V leads.

DISCUSSION

Diabetic acidosis and coma may be simulated by acute coronary thrombosis. A nondiabetic patient having an attack of myocardial infarction may temporarily show glycosuria which is entirely precipitated by the infarction. In the case reported here there was an associated acidosis with acetone in the urine and a lowered CO_2 combining power of the blood. When such findings accompany a state of semi-stupor, one is tempted to regard the condition as diabetic coma and to start insulin therapy. Insulin, however, may be harmful to patients with coronary disease. Even when the concentration of blood sugar is high, only small doses of insulin should be used unless it is certain that diabetic coma is present (2).

Atrial flutter, noted in the early phase of the acidosis in our case, is rare in myocardial infarction. It was replaced by normal sinus rhythm after the use of insulin, digitoxin and Dicumarol. Atrial flutter due to digitoxin intoxication is also rare (3), and was ruled out in our patient, as she had received no form of digitalis previously. It is possible that hyperglycemia triggered the atrial flutter, but this is speculative since the flutter occurred without reference to the hyperglycemia. The flutter was probably caused by strong vagal stimulation and by factors that disturbed the stability of the resting cardiac cells, such as anoxia or

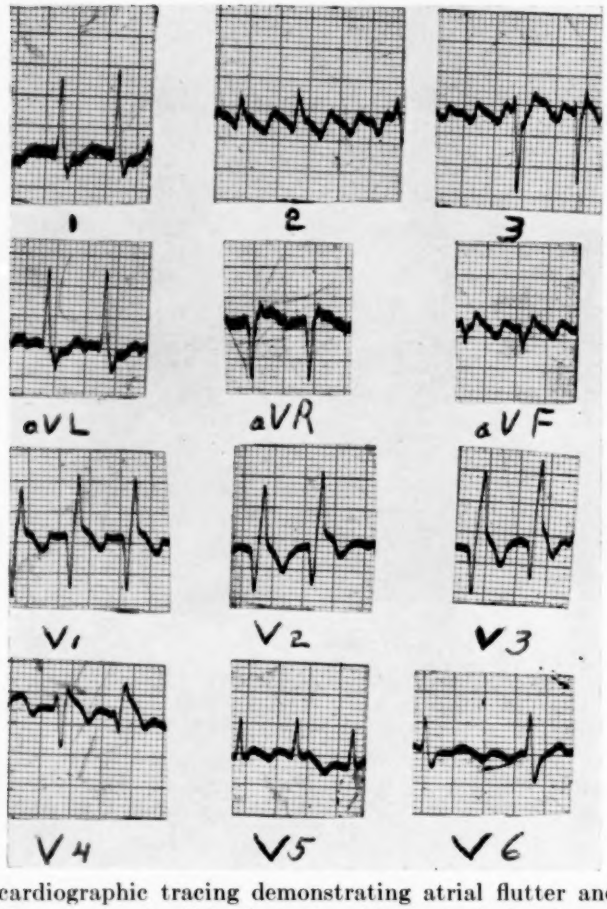

FIG. 3. Electrocardiographic tracing demonstrating atrial flutter and myocardial in farction with tall R waves in the V-leads 1, 2 and 3, typical of right ventricular hypertrophy.

any electrolyte changes tending to disturb the resting potential of the cardiac cells (4).

Idiopathic right ventricular hypertrophy was entertained as a diagnosis because of the tall R waves in the V leads 1, 2 and 3 (Fig. 3). Idiopathic hypertrophy of the right ventricle is largely a disease of females and is associated with right heart failure, cyanosis, pulmonary hypertension and electrocardiographic evidence of right ventricular strain, with or without right atrial enlargement and right bundle-branch block (5). When the blood sugar level had been reduced, the second tracing (Fig. 4) showed a normal sinus rhythm replacing the atrial flutter, a horizontal cardiac position, and persistent Q waves in the V leads 1, 2 and 3. There was no evidence of right ventricular hypertrophy; rather, the signs pointed to left ventricular hypertrophy.

Right ventricular hypertrophy is not transitory and could not revert to left ventricular hypertrophy in so short an interval, without roentgenologic evidence of a change in cardiac contour. In the case presented here (angina, diabetes mellitus, myocardial infarction) and even in other forms of heart disease, right bundle-branch block may come and go if the right bundle is involved in a zone

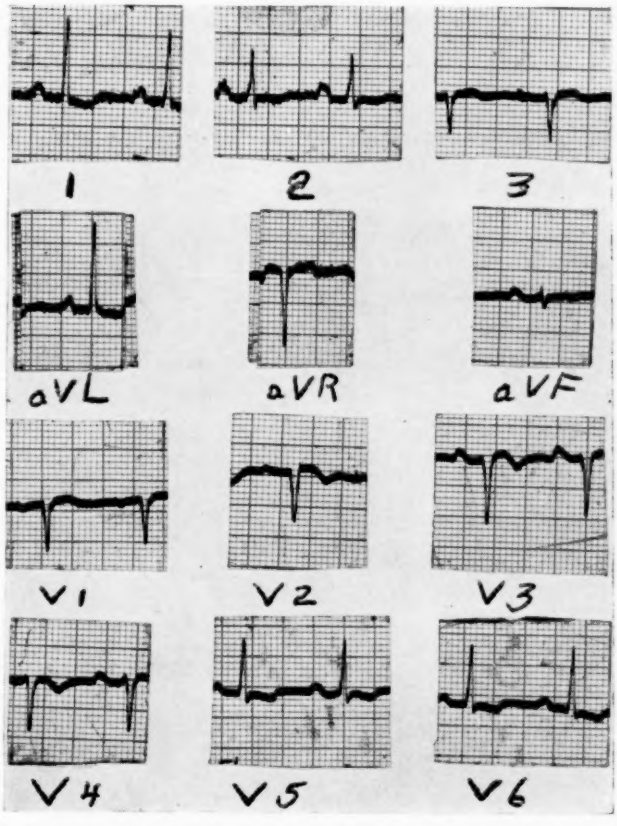

FIG. 4. Electrocardiographic tracing after treatment. Normal sinus rhythm has replaced the atrial flutter. No R waves in V leads 1, 2 and 3.

of ischemia or inflammatory edema. Its conductivity at any given time is affected by the degree of ischemia present at that time, since the conductivity is depressed but not abolished (6). The bundle is able to conduct when the cycle length is long enough to allow for the increased time needed for the bundle to recover. Accordingly, incomplete right bundle-branch block may appear when the rate is increased and disappear when the rate is diminished. Once bundle branch block is abolished by slowing the rate, it may remain absent after the heart rate has again increased to a rate with which the block was originally present (7). In the presence of coronary atherosclerosis with a rapid ventricular rate, coronary flow can be impaired sufficiently to produce an incomplete right bundle-branch block. This would account for the prominent R waves in V 1, 2 and 3. Following restoration of the normal sinus rhythm in Patient M. Y., the incomplete right bundle-branch block disappeared and normal S waves appeared in the first three V leads. The prominent R waves in the V leads 1, 2 and 3 (Fig. 3) did not indicate right ventricular hypertrophy. However, right bundle-branch block is associated with right ventricular hypertrophy, but there is no criterion for differentiation between right bundle-branch block and right ventricular hypertrophy (8).

Spodick and Littman recently reviewed 72 cases and presented 8 cases of

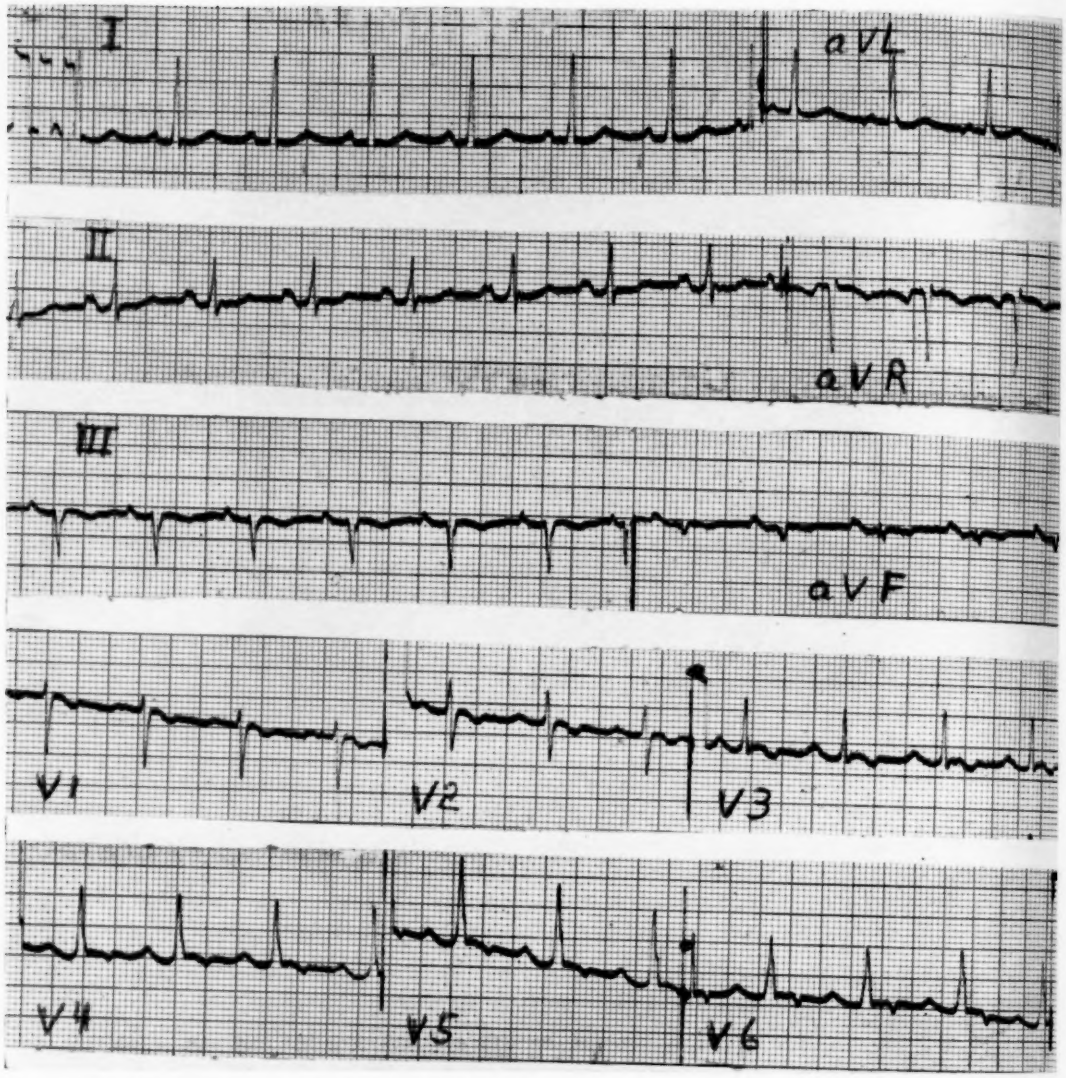

FIG. 5. Electrocardiographic tracing after further treatment, indicating horizontal heart. There are upright T waves in lead 1, with counterclockwise rotation in lead V_2.

idiopathic myocardial hypertrophy (9). This syndrome is characterized by left ventricular hypertrophy with or without varying degrees of mural fibrosis. The etiology is obscure, but it is observed to occur in previously healthy persons who have no valvular lesions and the course is usually rapid. In the 72 cases reviewed, there were various electrocardiographic patterns including nonspecific T wave changes, left bundle-branch block, myocardial infarction, various arrhythmias, and right ventricular strain (1 case), but none indicating right bundle-branch block. Of their own 8 patients, none had glycosuria or hyperglycemia, nor was there any evidence of right bundle-branch block, either transient or incomplete.

In the case reported here, the absence of valvular, congenital or hypertensive heart disease and the presence of electrocardiographic findings consistent with

those seen in idiopathic myocardial hypertrophy indicate a diagnosis of idiopathic myocardial hypertrophy associated with diabetes mellitus.

SUMMARY AND CONCLUSIONS

Routine determination of the blood sugar level should be carried out in all patients having a myocardial attack, as nondiabetic patients may temporarily show glycosuria which is entirely due to the cardiac episode.

In the case presented, the patient had been given an injection of morphine for relief of myocardial pain. Her semistuporous condition was mistakenly thought to be due to the morphine, whereas it was due to diabetic acidosis. Atrial flutter, though rarely seen in myocardial infarction, was noted during the early phase of the acidosis. Recognition and differentiation of right ventricular hypertrophy and right bundle-branch block created diagnostic problems.

In view of the persistent electrocardiographic pattern of left ventricular hypertrophy and the absence of roentgenologic or other evidence of valvular, congenital or hypertensive heart disease, this case appeared to be one of idiopathic myocardial hypertrophy associated with diabetes mellitus.

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SENILE OSTEOPOROSIS: TREATMENT WITH A STEROID HORMONE COMBINATION

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With advancing age, a decline in the endogenous production of anabolic steroid hormones by the gonads and adrenal cortex is to be expected. It is now firmly established that this deficiency in hormone production is associated with a defect in osteoblastic activity which, in turn, accounts for the inadequate building of bone in these later years (1–4). Steroid hormone insufficiency, which is so common in postclimacteric and elderly persons, is a primary factor in the pathogenesis of the specific metabolic bone disease termed osteoporosis. This insufficiency seriously impairs the physiologic activity of the osteoblasts and consequently the production of protein osteoid or the matrix of osseous tissue. Osteoporosis has therefore been characterized primarily as a disturbance in protein metabolism (1, 5). The associated disturbances in calcium and phosphorus metabolism assume secondary importance in the production of too little calcified bone. It is the production of too little matrix upon which mineral materials may be deposited which accounts for the failure to maintain a normal growth rate of newly forming bone. This condition is the direct cause of the derangement in dynamic balance between bone formation and bone resorption.

With advancing years, limitations of physical activity or complete disuse because of confinement to bed may superimpose or initiate new pathologic lesions in the bones. Mechanical stresses and strains to which the skeleton is subjected by normal physical activity is unquestionably a major stimulus to the deposition of bone matrix by the osteoblasts. Economy dictates that only those portions of the skeletal structure be maintained that are actively at work; thus in a patient confined to bed or restricted in movement, loss of bone matrix and minerals may be expected and, eventually, loss of bone density and strength. The elderly person, deficient for some years in anabolic gonadal and adrenocortical hormones and partially or wholly immobilized by arthritis, heart disease, hypertension or other geriatric disorders, will manifest the predominance of catabolic influences on bone physiology by the progressive development of generalized osteoporosis. Active loading or stressing of bones in these cases is not a realistic approach to restoring normal osteoblastic function. For the treatment of postclimacteric and senile osteoporosis, institution of a definite plan of steroid hormone therapy to stimulate protein anabolism is both feasible and beneficial (1, 3, 6–12).

In particular, combinations of androgen and estrogen have been found effective for inhibiting the osteoporotic process (6–14) by providing an additive

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metabolic activity without specific sexual effects. The response obtained in postclimacteric and senile types of osteoporosis has been impressive. This report concerns our experience with such therapy.

MATERIAL AND METHODS

The hormonal preparation use was a long-acting, balanced, androgen-estrogen combination (Deladumone).[1] It was administered intramuscularly, using a small-gauge needle. Each milliliter of this preparation contains 90 mg. of testosterone enanthate and 4 mg. of estradiol valerate in sesame oil. In addition to the greater anabolic potential of combined androgen and estrogen therapy and the advantages of balanced proportions, the prolonged action of the component steroids reduces the necessity for injection to once every two to four weeks.

The study was carried out with 54 elderly residents at the Menorah Home and Hospital for the Aged and Infirm during the period January 9, 1957-September 1, 1958. Ranging in age from 67 to 91 years, the patients were selected on the basis of roentgenographic evidence of mild to severe osteoporotic changes. As might be anticipated from the findings of other investigators, the frequency of osteoporosis was greater in females than in males; thus this series included 46 females and 8 males. The clinical status of these patients is outlined in Table 1. Twelve were ambulatory, whereas 42 were confined to the infirmary and therefore were either partially limited in physical activity or completely at bed rest. Several intercurrent disorders common to this age group, including hypertension, arteriosclerosis, heart disease, osteoarthritis, diabetes, hemiplegia, secondary anemia and carcinoma were also present, and 8 patients died during the course of this study.

Detailed laboratory and x-ray examinations were undertaken because of major complaints of pain in the back and legs, stiffness in the joints, weakness, poor appetite, or subjection to prolonged bed rest and inactivity. Once a well-defined osteoporosis was diagnosed, the patient was put into either the treatment or the control group.

Twenty-seven patients (22 females and 5 males) were given injections of 1 to 2 ml. of androgen-estrogen combination (Deladumone) every two to four weeks for a period of four months, after which treatment was standardized at a level of 1 ml. every four weeks. In addition, a high-protein diet and an ample intake of vitamin and iron supplements were prescribed.

A control group of 27 patients (23 females and 4 males) showing approximately identical osteoporotic involvement received no special treatment.

All patients were allowed to continue their usual medications for concurrent disorders and consequently received salicylates, assorted hypnotics and tranquilizers, digitalis, diuretics and antispasmodics.

Both subjective and objective signs of improvement were employed as a yardstick of the efficacy of the treatment. These criteria included relief of pain, improvement in well-being, increased range of motion, and roentgenographic evidence of increased density in the involved skeletal areas.

RESULTS

Anabolic steroid therapy produced distinct ("good") relief of pain, difficulty in motion, and weakness in 14 of the 27 patients, and fair relief in 8. In contrast, there were practically no changes in the control group (Table 2). Although roentgenographic evidence of accelerated bone formation is often difficult to demonstrate, in 6 cases the roentgenograms showed a definite increase in bone density attributable to new calcium deposits in osteoporotic regions. Roentgenograms in the control group showed relatively unchanged osteoporosis. During

[1] Deladumone was kindly supplied by E. R. Squibb & Sons, New York, N.Y.

TABLE 1

Clinical Status of 54 Patients with Senile Osteoporosis

	Years of Age	No. of Patients
Age distribution	65–69	4
	70–74	5
	75–79	22
	80–84	18
	85 and over	5

	No. of Cases		No. of Cases	
Intercurrent disorders	Hypertension	31	Hyperthyroidism	2
	Arteriosclerosis	42	Secondary anemia	29
	Cystitis	12	Diabetes	11
	Osteoarthritis	32	Carcinoma	5
	Bronchitis	7	Paget's disease	4
	Inactive tuberculosis	3	Hemiplegia	11
	Parkinson's disease	7	Malnutrition	8
	Heart disease	17		

		No. of Cases
Major complaints	Pain in back and legs	40
	Stiffness and difficulty in motion	4
	Weakness	16
	Poor appetite	24
	Prolonged bed rest or inactivity	10

		No. of Patients in which		
		Low	Normal	High
Laboratory findings	Red blood cell count	29	24	1
	Serum calcium level	1	47	6
	Serum phosphorus level	1	50	3
	Alkaline phosphatase level	6	47	1
	Sedimentation rate	—	42	3

		Deladumone Series	Control Series
Severity of osteoporosis (x-ray evidence)	Mild	4	3
	Moderate	5	7
	Severe	18	17

the period of investigation, 8 cases of fracture of the femur were recorded, *all in the untreated control patients.* No new fractures occurred in the group treated with the steroid combination (Table 2). However, repeated and close study of roentgenograms of the spine revealed unknown and previously undiagnosed compression fractures in 14 patients, of which 8 were in the treated and 6 in

TABLE 2

Clinical Response of Patients with Senile Osteoporosis to Anabolic Steroid Therapy with Deladumone

Series	No. of Patients	Relief of Symptoms			X-ray Evidence of Improvement	New Fractures (femur)
		Good	Fair	Poor		
Deladumone	27	14	8	5	6	0
Control	27	0	0	0	0	8

the control group. In 2 patients, previous fractures of the humerus were also discovered. What relationship these fractures bore to the initiation of hormone therapy could not be ascertained.

Deladumone was generally well tolerated and acceptable to the patients. A highly satisfactory response was obtained with a relatively low dosage and infrequent injections. There was a notable absence of undesirable masculinizing or feminizing effects which often limit the usefulness of androgenic or estrogenic preparations.

In the series of elderly patients reported here, this steroid combination proved a practical means of treating the osteoporosis associated with advancing years. In view of the fact that many of these patients were nonmobile, and that all had a negative nitrogen balance and poor protein intake, the benefits obtained were impressive. Ease of administration and the absence of unwanted sexual effects obviated some of the complications which have prevented the more extensive use of gonadal hormones to promote new bone formation. Since osteoporosis is a disturbance in protein synthesis, it is most suitably treated with a balanced dosage of androgens in combination with estrogens, plus a nutritious high-protein diet. Whenever possible, in addition, active loading or stressing of the skeleton should be encouraged as a necessary stimulus to osteoblastic activity.

DISCUSSION

Osteoporosis in the elderly person presents for consideration two primary therapeutic aspects. A postclimacteric decline in the endogenous production of anabolic gonadal and adrenocortical steroid hormones underlies a disturbance in protein metabolism which affects the formation of the matrix of osseous tissue. Superimposed may be osteoporosis due to partial or total disuse of the skeleton induced by restricted mobility or confinement to bed for any reason. Normally, physical activity is the greatest single stimulus to the laying down of new bone matrix in sufficient quantity for calcification and the maintenance of skeletal integrity and strength. In the elderly there is little potential for adequate physical activity and sufficient application of stress to the bones in order to induce more normal osteoblastic function. Once senile osteoporosis is well established, the mere stress of weight-bearing rather than a distinct traumatic experience may easily lead to fractures of the lower extremities, particularly the femur.

The most widely applicable and most effective form of management of postclimacteric and senile osteoporosis centers about a general program of anabolic steroid therapy, using an androgen-estrogen combination. Our experience with a well-balanced dosage of androgen and estrogen (Deladumone) indicates that fair to good relief of pain and improvement in well-being can be achieved in a significant proportion of cases. In 6 of 27 patients, roentgenographic evidence of increased bone density as a result of new calcium deposits in osteoporotic regions was observed, whereas in a control group there was no visible change in either symptomatology or bone pathology. Clinical benefits were obtained with a relatively low dosage and infrequent injections. During the twenty-one months in which this investigation was carried out, there was no evidence of unwanted sexual effects. In addition to this type of steroid therapy, a nutritious high-protein diet and ample quantities of vitamin and iron supplements were prescribed.

SUMMARY

A practical approach to the treatment of osteoporosis in the postclimacteric or senile patient involves administration of an anabolic steroid hormone combination, a high-protein diet, and an adequate amount of vitamins and iron.

In a series of 27 patients confined to a home for the aged, administration of a balanced androgen-estrogen combination (Deladumone) effected the desired improvement in symptomatology and, in some cases, stimulated the deposition of calcium in osteoporotic bone. No change in osteoporosis or symptoms was observed in a control group of 27 patients. The steroid combination was given in a single injection every two to four weeks and was well tolerated over a period of twenty-one months. No masculinizing or feminizing manifestations were observed.

This experience would indicate that use of such a balanced androgen-estrogen combination is an effective method of stimulating protein anabolism and therefore a valuable therapeutic agent in combating the unfavorable catabolic influences which tend to predominate with advancing age. It is an uncomplicated and widely applicable means of treating postclimacteric and senile osteoporosis.

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GERIATRICS. (REVIEW OF PSYCHIATRIC PROGRESS 1959.)
Bowman, K. M., and Engle, B. *Am. J. Psychiat.* **116:** 629 (Jan.) 1960.

1. Ataractic drugs reported on favorably in the treatment of elderly psychiatric patients under controlled conditions and without undesirable side-effects include hydroxyzine, buclizine, and methylphenidate hydrochloride. Tranquilizers were successfully combined with a vitamin-hormone stimulant in Ritonic and with a nutritional-hormone supplement in Neobon. 2. Diphenhydramine hydrochloride (Covatin) was ineffective in elderly female patients and pentamethylenetetrazol in senile patients under controlled conditions. 3. Procaine hydrochloride proved to be no panacea but only a mild activator of the pituitary-adrenal system. 4. Tofranil in a dosage of 250 mg. daily caused coarse tremor in the limbs of elderly psychiatric patients. 5. Two reports indicated that vitamin B_{12} deficiency may be the cause of senile dementia and confusional states. 6. Mild to moderate protein depletion and negative nitrogen balance were found in 32 patients 62 to 89 years of age who were studied for eight to ten months. 7. A study of 59 men aged 55 to 65 years showed that age was not necessarily accompanied by a change in the cerebral blood flow and cerebral metabolism, and that demonstrable changes in mental abilities were much smaller than those previously reported. 8. The majority of biologic, genetic, cultural, and psychologic factors favor females over males in health and longevity. 9. The serum cholesterol level, the frequency of arcus senilis, and the incidence of coronary artery disease were much higher in men with an intense drive for achievement who were continually involved in competitive efforts than in those with the converse pattern. 10. An increase was apparent in the use of psychotherapy in geriatric patients; supportive approaches and active therapy predominated over insight therapy. 11. The Wechsler Adult Intelligence Scale, established on 352 subjects in Kansas City, was tested on 130 normal subjects aged 60 to 70 years and on 32 mental hospital patients. The results—a higher verbal than performance IQ score in 82 per cent except for the hospitalized group aged 70 to 74—contradicted the Wechsler standards taken as the national norms. Therefore, Eisdorf, Busse and Cohen question the generality of this sample as the basis for the national norms. 12. Upon re-examination of Army Alpha test scores taken in 1950 on 127 men who took the tests in 1919, both increases and decreases in scores were found but the changes were not related to initial ability levels. Age had not been more kind to the gifted few. 13. A paired-associate learning test given to 18 elderly psychiatric patients and a control group was sensitive to memory impairment without dependence on intellectual functioning. 14. In a comparative performance test, stimuli from varying numbers of significant sources were presented for simple reaction time. The performance of younger subjects did not seriously deteriorate until the number of significant sources reached 8, whereas that of older subjects deteriorated when the number of alternative sources increased from 1 to 2.

MODIFICATIONS VASCULAIRES OBSERVÉES DANS LE POUMON DU VIEILLARD (VASCULAR MODIFICATIONS OBSERVED IN THE LUNGS OF OLD SUBJECTS).
Delarue, J.; Chomette, G.; Auriol, M., and Abelanet, R. *Arch. anat. path.* **6:** 295, 1958; through Excerpta med. (Gerontol. & Geriatrics) **2:** 386, 1959.

This anatomic study is based on examinations of 27 sets of lungs of persons over 70 years of age. Histologic examination and teleradiography of organs after injection of the bronchial vascular system were used. The bronchi show signs of atrophy, accompanied

frequently by dilatation and almost always by inflammation. The parenchyma shows signs of emphysema. The pulmonary artery lesions include multiple sclerosis intermingled with anthracosis with or without thrombosis, foci of antheroma, and proliferating endarteritis in the segments of medium or small caliber. On the other hand, there is hyperplasia of the bronchial arterial system with a strongly developed systemic network. Retrograde filling of the pulmonary arterial system is constantly present, but its degree varies from one case to another. Sometimes there are large communications between the two arterial systems of the lung. The systemic hypervascularization is in many cases, but not in all, dependent upon the modifications of the pulmonary arteries (thromboses) or upon bronchial alterations (bronchiectases).

THE USE OF POLYSORBATE-80-CHOLINE-INOSITOL COMPLEX IN THE TREATMENT OF HYPERCHOLESTEREMIA.

Edwards, R. V. *J. Florida M. A.* **5:** 565 (Nov.) 1959.

A complex known as Monichol contains 500 mg. of polysorbate-80, 500 mg. of choline dihydrogen citrate, and 250 mg. of inositol in each 5 ml. The complex was administered to 21 ambulatory patients aged 39 to 70 years. The diagnoses among them were: arteriosclerotic heart disease with angina and with or without previous cardiac infarction, arteriosclerosis obliterans, generalized arteriosclerosis, idiopathic hypercholesteremia, essential hypertension, familial hypercholesteremia, and exogenous obesity. Initially, 17 patients had cholesterol levels above 300 mg. per 100 ml.; 4 patients had levels below 300 (range 235 to 610 mg. per 100 ml.). The dosage was 10 ml. twice daily for an average of seven months. In addition, 1 patient with a serum cholesterol level above and 1 patient with a level below 300 mg. per 100 ml. adhered to a rigid low-fat diet for prolonged periods. The results of therapy were favorable in 19 patients, and minimal in 2. Sixteen of the 17 patients with high initial cholesterol levels had a marked reduction; the one whose level was reduced from 330 to 307 mg. per 100 ml. took only half of the prescribed dosage. Favorable results were obtained in 3 of the 4 patients with levels initially below 300. The fourth patient had a reduction of 28 mg. In the preceding seven months, this patient had not responded to a low-fat diet and thyroid therapy. The average reduction in the series was 84 mg. (range 23 to 188). The greatest reduction in the shortest time was from 330 to 190 mg. per 100 ml. in one month in 1 patient. When the dosage was cut by half in 2 patients, the serum cholesterol levels increased so that restoration of the original dosage became necessary. It was apparent that the dosage should be maintained constantly at 10 ml. twice daily. The serum cholesterol levels in both patients receiving low-fat diets declined significantly in thirteen and six months, respectively (320 to 135 mg. per 100 ml., and 235 to 195 mg. per 100 ml., respectively). Polysorbate-80-choline-inositol complex affords a practical means of reducing serum cholesterol concentration. It permits full cooperation of the patient, and a rigid low-fat diet is unnecessary.

SEXUAL POTENCY IN AGING MALES. III. TECHNIC OF AVOIDING NERVE INJURY IN PERINEAL PROSTATIC OPERATIONS

Finkle, A. L., and Saunders, J. B. DeC. M. *Am. J. Surg.* **99:** 23 (Jan.) 1960.

Attention to specific anatomic considerations and some essential operative steps in perineal prostatectomy may help to preserve sexual potency. In the perineal approach to the prostate, the levator ani must be dissected off Denonvillier's fascia in order to expose the posterior surgical capsule of the prostate. Injury to the major parasympathetic nerve fibers may occur if exposure of the distal ends of the seminal vesicles is sought, either in an attempt to widen the operative field for enucleation of the gland, or for radical prostatectomy. A technic is described for avoiding such injury. A sharp lateral transection of Denonvillier's fascia between the distal ends of the seminal vesicles at or immediately proximal to the base of the prostate is to be avoided, as this leads inevitably to damage of the para-

sympathetic fibers. Instead, *blunt* dissection of the space between the rectum and the base of the prostate should be carried out. The separation of the anterior and posterior layers of the fascia is accomplished by blunt dissection. The rectum is depressed with a sponge held in a sponge stick, thus exposing the base of the prostate and the rectum. A similar instrument (a "cherry" or "peanut") is used to elevate, gently and stepwise, the fascia as it covers the base of the prostate and the distal ends of the seminal vesicles. This maneuver separates the layers of fascia. At this point, posterior and lateral retractors may be inserted or progressive dissection or transection made for the particular operation planned.

RHEUMATOID PULMONARY DISEASE. REPORT OF A CASE.

Flatley, F. J. *New England J. Med.* **261:** 1105 (Nov. 26) 1959.

In a 62-year-old patient with rheumatoid arthritis, pneumonitis, and recurrent pleural effusions, joint pain did not completely disappear despite treatment with gold, salicylate, vaccine and adrenocortical steroids. The patient noted increasing cough, weakness, malaise, fever and shortness of breath associated with an exacerbation of joint symptoms. Pleural effusion and infiltration of the left lower lobe were seen roentgenographically. When this lobe had been resected, the lung showed marked fibrous thickening of the pleura and one large and several small subpleural nodules with the histologic appearance of rheumatoid nodules. A diffuse fibrosing interstitial pneumonitis with focal areas of organizing pneumonia surrounded the nodules. The pulmonary fibrosis appeared to be progressive. On the basis of these rheumatoid nodules with fibrinoid necrosis in the lung and the character of the associated symptomatology, as well as the absence of evidence for other etiologic factors, this was considered to be a case of rheumatoid pulmonary disease. Exacerbation of joint pain and pleural effusion requiring thoracentesis occurred seven months postoperatively. Thereafter the rheumatoid arthritis was well controlled with corticosteroid therapy and the patient had no further pulmonary symptoms. The right-sided hydrothorax decreased slightly, and there were no further pulmonary parenchymal changes. Rheumatoid pulmonary disease must be considered in the differential diagnosis of pleural and pulmonary lesions that occur in patients with rheumatoid arthritis.

THE ETIOLOGY OF SENILE ENTROPION.

Fox, S. A. *Am. J. Ophthalmol.* **48:** 607 (Nov.) 1959, Part 1.

Senile entropion is not caused by spasm but by the same senile degenerative processes as senile ectropion. It differs in that a relatively intact tarso-ligamentous sling is maintained. Repair is best accomplished by strengthening the tissues of the lid horizontally by vertical excision. The technic is described. Since senile entropion is the result of aging, no procedure will effect a permanent cure in all cases.

L'ASPECT HÉMATOLOGIQUE DE LA VIEILLESSE. III. LA MOELLE OSSEUSE (THE HEMATOLOGIC PICTURE IN OLD AGE. III. THE BONE MARROW).

Gingold, N.; Cutcudache, C.; Goresco, I., and Podhorschi, A. *Sang* **29:** 243, 1958; through Excerpta med. (Gerontol. & Geriatrics) **2:** 391, 1959.

In each of 65 patients, one or more sternal punctures were performed. In 55 cases (87 to 75 per cent) the paucity of cells in the marrow was striking; maturation of the leukopoietic system was inhibited or arrested in 71.3 per cent, and that of the erythropoietic system in 72 per cent. Thirty-eight cases showed lymphocytosis of the bone marrow, together with lymphopenia of the peripheral blood. Accumulation of reticular elements was found in 17 cases and of mast cells in 15.

L'ASPECT HÉMATOLOGIQUE DE LA VIEILLESSE. II. LE SANG PÉRIPHÉRIQUE. (THE HEMATOLOGIC PICTURE IN OLD AGE. II. THE PERIPHERAL BLOOD).

Gingold, N.; Podhorschi, A.; Cutcudache, C.; Enache-Ciuntu, F., and Balan, A. *Sang* **29:** 237, 1958; through Excerpta med. (Gerontol. & Geriatrics) **2:** 390, 1959.

The findings in 80 persons (29 men, 51 women) from 60 to 106 years of age are reported. The erythrocyte counts were normal or slightly below normal; the hemoglobin content was markedly reduced. The numbers of reticulocytes and thrombocytes were normal, the serum iron content lower. In comparison with normal adults, the qualitative blood pictures showed more atypical elements (Türk's and Rieder's cells, plasma cells, lympho-reticular elements) and more morphologic changes in the erythrocytes and leukocytes (such as anisocytosis, poikilocytosis, anisochromia, macrocytosis, microcytosis, hypersegmentation or pathologic granulation), whereas sex differences were less marked. Evaluation of the findings was based on calculated mean values. The individual values showed a fairly wide range.

"GEHEILTE" NIERENTUBERKULOSE ("HEALED" RENAL TUBERCULOSIS).

Gloor, H. U. *Schweiz. Ztschr. Tuberk.* **16:** 165, 1959; through Ciba Literature Review **4:** 394, 1959.

The use of chemotherapeutic agents has resulted in a decrease in the number of nephrectomies performed on account of tuberculosis. It is now possible to promote scar formation and to inactivate the foci within only a few years and thus to avoid a premature, irreversible operation. Complete transformation of the specific tissue into a lymphoplasmacellular structure is proof that the tuberculous infection has been entirely overcome. Gloor managed to achieve inactivation of the foci in 45 of 132 cases of renal tuberculosis. No relapses have occurred for more than six years in the 8 patients with an intraparenchymatous form of the disease who were treated for two years. In the 11 patients with small abscesses of the renal calyx, scar tissue persisted for over four years in 9 cases. When no complications have set in after such a long period of observation, tuberculostatic medication may be discontinued. In patients with extensive and even bilateral destruction of papillae or calyces, accompanied by cavitation (26 cases), the regression, as revealed by the roentgenogram, took two main forms, "amputation" of the calyx, which continues to be regarded as an "inactivated process," and complete disappearance of the foci together with re-epithelization, which can be considered a real cure. The favorable results were obtained by administering tuberculostatics and various specific chemotherapeutic agents, including Vionactane, and for a long time.

PROBLEMS OF ANTICOAGULANT THERAPY IN CEREBROVASCULAR DISEASE.

Groch, S. N.; Hurwitz, L. J.; McDevitt, E., and Wright, I. S. *Neurology* **9:** 786 (Nov.) 1959.

Anticoagulants were used to treat cerebrovascular disease in 108 patients, the majority of whom were over age 50 years. Forty-seven patients required therapy and 61 were selected by randomization. Therapy was discontinued in the hospital in 54 patients as follows: died, 18; bleeding complications, 14; transferred, 16; inability to attend, 4; social problem, 2; death from complications of anticoagulant therapy, 2; death from other causes, 1. It was discontinued by the end of three months in more than half of these. Forty-eight patients continued as outpatients, and 6 remained in the hospital. Among those in whom therapy was discontinued while attending the clinic, 42 per cent were past age 71. Bleeding necessitating discontinuation of therapy occurred in 1 of 18 patients followed for more than twelve months. In the over-all series, hemorrhagic complications occurred in 22 patients (20 per cent) and included 2 deaths (2 per cent), 6 severe complications (6 per cent), 6 mild complications (6 per cent), and 7 associated with unrecognized pathologic states such as carcinoma of the colon. The incidence of complications was 26 per cent among patients in whom therapy was obligatory and 16 per cent among those selected by randomization. The

incidence of complications also was greater in older patients. However, 8 patients past the age of 60 were able to attend clinic for more than twelve months. Severity of complications was not correlated with age. No clear association was apparent between bleeding complications and the presence of moderate hypertension. Prothrombin time determinations were made weekly in the majority of patients and biweekly in a few. In long-term anticoagulant therapy, the prothrombin time will fall below the minimum of 25 seconds or exceed the upper limit of the therapeutic range so frequently that continuous protection cannot be assumed. Two pitfalls were the too ready acceptance of a bloody spinal fluid as traumatic, and failure to heed the warning of a xanthochromic spinal fluid. Anticoagulant therapy is feasible for cerebrovascular disease but its use involves risks and problems. Abrupt discontinuation is hazardous and may result from the whim of the patient or from inadvertence of the physician during intercurrent illness. The hazard of cerebral hemorrhage is always present. The known prognosis of a pattern of cerebrovascular disease must be weighed. Careful consideration must be given before administration and constant vigilance maintained throughout therapy.

POSTMENOPAUSAL UTERINE BLEEDING OF PSYCHOGENIC ORIGIN.

Heiman, M., and Shapiro, W. J. *Am. J. Obst. & Gynec.* **79:** 11 (Jan.) 1960.

Case reports are presented of postmenopausal uterine bleeding in 5 patients. Gynecologic examinations and findings afforded no explanation. The bleeding was concluded to have occurred on a psychogenic basis, since each bleeding followed the loss of, or separation from, a person loved by or important to the patient. Underlying certain cases of functional uterine bleeding is a depression. The bleeding is a somatic equivalent to a psychologic reaction of depression. Reassurance usually suffices unless the depression is profound, when psychiatric help is indicated.

CAROTID ARTERY OCCLUSIVE SYNDROME.

Hurwitz, L. J.; Groch, S. N.; Wright, I. S., and McDowell, F. H. *A.M.A. Arch. Neurol.* **1:** 491 (Nov.) 1959.

Variability in the clinical picture and prognosis in individual patients with carotid artery disease is illustrated by 57 cases. The deleterious effect may vary from minimal to catastrophic. A patient can have had a long history of cerebrovascular disease and yet have had a more or less normal life. Therefore, any procedure adopted in treatment should be one that is carefully controlled. A need exists for careful study of proposed therapeutic measures. In stroke with an acute catastrophic onset, large percentages of deaths and severe residual disabilities occur. In cases with this kind of onset, anticoagulant therapy and surgery do not give encouraging results. More emphasis should be given minor cerebrovascular episodes which precede stroke, as they may lead to the diagnosis. Following the patients provides an opportunity to study the natural course of the disease. Survival without symptoms or disability for at least a year may be expected in many patients with "small" strokes, irrespective of age. The diagnosis can be made clinically in many patients, but in some it can be made only with angiography or surgical exposure of the vessel. The most reliable procedures have been ophthalmodynamometry and, to a lesser degree, palpation of the carotid artery in the pharynx, used in conjunction with evaluation of signs and symptoms. In the reported series, maximum incidence was between ages 51 and 70 years. Males predominated in a 2:1 ratio. Seventy per cent of complete unilateral occlusions were localized in the neck. Complete bilateral occlusion occurred in 2 patients. Twenty-six per cent of the patients had a history of previous stroke from sixteen years to two weeks previously. Transient ischemic attacks occurred in 39 per cent from nine years to ten days before the presenting stroke. Repeated ipsilateral visual disturbance is of diagnostic significance; when contralateral symptoms appear, the diagnosis is almost certain. This symptomatology occurred in 18 per cent of the series. Other symptoms that

preceded diagnosis by more than a week included epilepsy in 2 patients, headache, and impaired mentation. Symptoms that occurred within seven days prior to the stroke included headache and somnolence in 7 patients each. The onset of stroke varied from sudden in 33 patients to an unexpected finding in 5 patients. The majority of occlusions (79 per cent) were presumed to be the result of atherosclerosis. Signs present at the time of diagnosis in decreasing order of frequency were aphasia, coma, impaired mentation, and somnolence. Dysfunction in motor and sensory perception was present in 86 per cent. Fourteen patients died during hospitalization, 1 following internal carotid endarterectomy and 3 as a consequence of the carotid occlusion. All 17 patients with a mild motor deficit recovered. Of the 32 with a moderate or severe deficit, 5 recovered, 8 had a partial recovery, and 7 did not recover. The remainder with a moderate or severe deficit died. Aphasia was the neurologic sign least likely to clear during the acute attack. The presence of prolonged coma and of severe cardiac disease was associated with a poor prognosis. Forty patients remained untreated, 6 had a cervical ganglionectomy, and 11 received anticoagulants for four months or more. Transient ischemic attacks ceased in the treated patients, but also in 5 patients without therapy. Among the 43 patients who survived the acute attack, 5 subsequently died (4 of heart disease), 2 had a recurrent stroke (1 with recovery), 1 had a myocardial infarction with recovery, and 5 could not be followed. Of the other 30, 3 have rare epileptic seizures, 15 are able to work, 5 have some intellectual impairment, 10 have moderate to severe hemiplegia, and 6 have aphasia. The survival time after the stroke has been five years for 9 patients, two years for 20 patients, and one year for 27 patients.

CLINICAL EVALUATION OF TRIMETHIDINIUM METHOSULFATE. A NEW GANGLIOPLEGIC AGENT.

Janney, J. G., Jr.; Caciolo, C.; Duane, G. W.; Reddy, S. R. V., and Simonidis, A. K. *Am. J. Cardiol.* **4:** 745 (Dec.) 1959.

Trimethidinium methosulfate, a new vasodilator drug which acts through its ganglionic blocking effect and through central action, was tested in 20 patients with hypertension for an average period of nine months. The drug produced a significant response in 85 per cent of the cases, 55 per cent becoming normotensive. The reduction in the average blood pressure levels was 57 mm. Hg systolic and 27 mm. Hg diastolic. Since most of the patients had been treated previously with pentapyrrolidinium, it was possible to compare the two drugs. Trimethidinium methosulfate showed a better and more consistent hypotensive effect, greater and more rapid reduction in severity index, and although side-effects were more frequent, they were less severe and more easily controlled. Comparison of the results with trimethidinium with those reported in the literature for pentapyrrolidinium and mecamylamine shows the control of blood pressure to be at least as good or better and the side-effects to be less severe and more manageable.
(Authors' summary.)

CRITICAL STUDY OF THE RELATIONSHIP BETWEEN ANGINA PECTORIS AND CORONARY ATHEROSCLEROSIS.

Lenègre, J., and Himbert, J. *Am. Heart J.* **58:** 539 (Oct.) 1959.

The reliability of angina pectoris as a clinical criterion for the presence of coronary atherosclerosis was assessed from the records of 188 cases of angina pectoris. Typical angina pectoris was present in 160 cases, and atypical angina pectoris (suspected or questionable) in 28 cases. Occlusion or stenosing atherosclerosis was present in (a) 80 per cent of the entire group, (b) in 87 per cent of those with typical symptoms of angina pectoris, (c) in 93 per cent of 146 cases of angina not associated with factors of heart disease (syphilitic aortitis, valvular disease, chronic lung and bronchial disease, auricular fibrillation) except for

hypertension, (d) in 96 per cent of 60 cases when hypertension was also excluded (primary anginal cases), and (e) in 100 per cent of 52 cases remaining when clinically atypical cases, secondary cases, and those associated with other heart diseases were excluded (primary anginal cases, clinically typical). These correlations show the limits to the use of angina pectoris to detect atherosclerosis. It is necessary to select the cases for study in order to obtain greater accuracy in identifying underlying atherosclerosis. The records used in this study were obtained from 828 necropsy records of cardiac patients. The fact that the presence of angina is not perfect evidence that atherosclerosis exists is demonstrated by the finding of atherosclerosis at necropsy in 17 per cent of 640 patients who during life had no suggestion of angina pectoris.

UEBER DIE GLUKAGON-PROBE BEI LEBERKRANKHEITEN UND BEI DIABETES MELLITIS (GLUCAGON TEST IN LIVER DISEASES AND DIABETES MELLITUS).

Linke, A. *Klin. Wchnschr.* **37:** 876, 1959; through Ciba Literature Review **4:** 401, 1959.

Glucagon, the second hormone of the pancreas, causes glycogenolysis in the liver (not in the muscles) and thereby leads to hyperglycemia. The extent to which the blood sugar level rises is dependent upon the glycogen level in the hepatic cells. In view of these properties of glucagon, a test was evolved which has proved useful in liver diseases and in diabetes mellitus since it is the first liver function test to provide direct information about the glycogen content of the liver. The test is performed in the morning before breakfast with the patient lying down; a normal diet is given for three days prior to the test. The glucagon is injected intravenously in a dose of 2 gamma per kilogram of body weight and the blood sugar levels are measured at certain intervals. The glucagon injection provokes the release of increased amounts of insulin with the result that the blood sugar level falls temporarily below its initial value. As regards liver diseases—cirrhosis with decompensation, epidemic hepatitis at its climax, hepatic disorders due to hyperthyroidism, and liver damage caused by methyltestosterone respond with the smallest rise in blood sugar concentration. If insulin secretion is studied in the second part of the glucagon test, labile diabetes (due to insulin deficiency) can be distinguished from stable diabetes (due to old age) by examining the behavior of the blood sugar curve. The results also make it possible to draw certain conclusions as regards therapy.

SERUM CHOLESTEROL LEVELS IN HUMAN ATHEROSCLEROSIS.

Patterson, J. C.; Dyer, L., and Armstrong, E. C. *Canad. M.A.J.* **82:** 6 (Jan. 2) 1960.

Serum cholesterol determinations were carried out at least once a year on 800 ambulatory patients permanently confined to a hospital. The determinations were begun in 1953; by April 1959 there were 191 fatalities in the series. In each of these, the severity of atherosclerosis was determined at necropsy in four different arteries and using six different criteria. The mean antemortem serum cholesterol level for each patient was then compared with the severity of disease in his arteries, and with the presence or absence of those complications of atherosclerosis that can be detected at autopsy. Adequate numbers of cases for statistical analysis were available only in the seventh, eighth and ninth age decades. The results lend little support to the contention that the severity of atherosclerosis is related to the level of serum cholesterol, except perhaps when it exceeds 300 mg. per 100 ml. In 58 cases in the age group 60 to 69 years, significant relationships between the level of serum cholesterol and the severity of disease were found only once in 40 statistical analyses, and the complications of atherosclerosis were just as frequent in cases with low serum cholesterol levels (150 to 199 mg. per 100 ml.) as in cases with moderately high ones (250 to 299 mg. per 100 ml.). (From authors' summary and conclusions.)

OBSERVATIONS ON FLUMETHIAZIDE IN THE TREATMENT OF ESSENTIAL HYPERTENSION.

Rosenfeld, J. B.; Beem, J.; Brest, A., and Moyer, J. H. *Am. J. Cardiol.* **4:** 734 (Dec.) 1959.

Flumethiazide (Ademol) in a dosage of 500 mg. twice daily for two months produced a fall in mean blood pressure of more than 20 mm. Hg in 41 per cent of patients in the supine position. Twelve per cent became normotensive. A slight orthostatic effect was noted, in that 53 per cent responded when blood pressures were recorded in the upright position. Minimal side-effects were observed. The response to rauwolfia in a second group of patients was somewhat less than that previously observed in other series of patients. A significant additive effect on blood pressure was noted when rauwolfia and flumethiazide were given in combination, which was better when flumethiazide was the first drug given followed by rauwolfia, rather than when they were given in the reverse order. A significant reduction in blood pressure was obtained in 73 per cent of patients by the first procedure and in 64 per cent when rauwolfia was given first. An orthostatic hypotensive effect also was noted when flumethiazide was given in the combination. In none of the treated groups were there marked changes in the concentration of plasma electrolytes or blood urea nitrogen. The average plasma sodium level dropped slightly during administration of flumethiazide but did not change when combined therapy was given to the same group. When rauwolfia had been given first, the plasma sodium level increased slightly after two months of combined therapy. The mean plasma potassium level dropped slightly during flumethiazide administration but increased slightly when rauwolfia was combined with it and given to the same group. In patients who received rauwolfia first, the plasma potassium level dropped slightly after two months of combined therapy. A relationship between a decrease or increase in body weight and a decrease or increase in blood pressure was noted in 40 per cent of the patients, but was lacking in the remainder.

PRAKTISCH WICHTIGE BESONDERHEITEN DES KOHLENHYDRATSTOFFWECHSELS IM ALTER (PRACTICAL IMPORTANT PECULIARITIES OF CARBOHYDRATE METABOLISM IN ADVANCED AGE).

Seige, K., and Thierbach, V. *Münch. med. Wchnschr.* **100:** 2029, 1958; through Excerpta med. (Gerontol. & Geriatrics) **2:** 378, 1959.

Muscle is the locus of the major portion of carbohydrate metabolism. In aged persons the creatinine coefficient decreases to 50 per cent, while ATP sensitivity in muscle extract decreases at the same rate. Other centers of metabolism, the liver and pancreas, change anatomically by atrophy. This may be a cause of disposition to diabetes mellitus in aged subjects. Production of insulin decreases. In blood sugar curves, hyperglycemia increases in height and length of time after administration of glucose or starch, and this may become physiologically established. Extrapancreatic factors may also be contributing causes of prediabetic blood sugar levels. Aged persons show more sensitivity to peroral administration of sugar than to intravenous injections, and more sensitivity to insulin also. Activity of the adrenal cortex and the quantity of excreted glycocorticoids do not depend upon age. The therapeutic consequence of sugar administration is that preference should be given to fructose over other carbohydrates, as its metabolism is independent of insulin, and it is better tolerated by elderly people.

RUPTURE OF THE HEART IN MYOCARDIAL INFARCTION. CLINICAL AND PATHOLOGIC OBSERVATIONS.

Sigler, L. H. *Am. J. Cardiol.* **5:** 14 (Jan.) 1960.

Rupture of the heart in 8 cases of myocardial infarction and a review of the literature are presented. The condition appears to occur more often than the literature would indicate.

It affects an area of the heart where fresh myocardial damage is present, but never in areas of organized infarction. In the majority of patients it occurs in the free wall of the left ventricle, mainly in the anterolateral region close to the apex, and may involve portions of the lower interventricular septum. In occasional cases it may affect the interventricular septum alone and rarely it may be confined to the papillary muscle. One or more of the underlying predisposing causes are pre-existing and coexisting hypertension with its strain on the heart and hypertrophy of the myocardial fiber; the female sex, in whom hypertension is more frequent; the older age groups, in which the normal histologic structure of the myocardium is altered; an early age of the infarct; the effect of leukocytic infiltration with its local enzymatic destructive effect on the myocardium; and the location of the coronary occlusion usually in the anterior descending branch of the left coronary artery. The most important direct cause appears to be an aneurysmal-like expansion of the devitalized myocardium in the area of infarction during systole which produces a suction effect on the blood in that area. This probably causes overdistention and rupture of the arterioluminal and arteriosinusoidal vessels with dissection of blood through the myocardium. Pressure exerted by contraction of the adjacent normal heart muscle upon the devitalized area also causes tearing of the diseased myocardial tissue. The diagnosis of rupture of the free wall of the heart during life is hard to make, but in perforation of the interventricular septum the diagnosis is relatively easy to establish. Treatment of the condition when affecting the free wall should, therefore, be prophylactic. The condition must be borne in mind in any case of myocardial infarction especially when it occurs under the aforementioned circumstances, and careful management of the acute phase of infarction is to be instituted. In perforation of the interventricular septum, treatment should be symptomatic and directed toward heart failure. (From author's summary.)

A REVIEW OF DRUGS IN THE ELDERLY PSYCHIATRIC PATIENT.

Silverman, M.; Parker, J. B., and Busse, E. W. *North Carolina M.J.* **20:** 428 (Oct.) 1959.

Mental disturbances in elderly persons are classified according to the disabling symptomatology. Among the *chronic psychoses* are included chronic schizophrenia, chronic brain syndrome, involutional paranoid psychosis, and paranoid states in which loss of social discretion and weakening of defenses cause basic personality traits to become pronounced. Among drugs used in these states, chlorpromazine improves eating habits, sleep patterns, urinary incontinence, and personal hygiene and reduces agitation. From 74 to 93 per cent of patients improve in behavior. The response in chronic brain syndrome is inversely related to the degree of organic damage. Prochlorperazine benefits a high percentage of patients with mild to moderate anxiety, but only half of those with severe agitation. Meprobamate decreases angry outbursts, sleep disturbances, wandering, and fighting in senile psychoses. Reserpine, or methylphenidylacetate, or both, control overactive, underactive, and mixed behavior. Reserpine alone is usually used when overactivity predominates, whereas methylphenidylacetate is given to those with more negative characteristics. In various senile states, methylphenidylacetate sometimes improves the mental and physical status when reserpine has had no appreciable effect. Nicozol (phenylenetetrazol with niacin) combined with reserpine, a combination of reserpine with d-amphetamine and therapeutic vitamins (Vitarespital), and L-Glutavite also bring about improvement in elderly psychotic patients. Perphenazine is the drug of choice for the management of aggressive behavior in elderly patients. Preliminary experience suggests that trifluoperazine also may be of value in this group. Perphenazine is nonhypotensive and devoid of some of the side-effects that limit the use of other ataractic drugs, stimulants and sedatives. Its tendency to cause parkinsonism and dyskinetic syndromes can be overcome easily by lowering the dosage and using concomitantly a drug with activity against parkinsonism. *Psychiatric reactions* in the aged include tension states, affective reactions, and confusional states. Meprobamate controls both the subjective symptoms and objective signs in tension states. In affective reactions,

perphenazine counteracts the agitation but not the depression. It is the drug of choice in states of excitement and elation. Tofranil (imipramine hydrochloride) may relieve depression, but its hypotensive effect limits its use. Perphenazine also controls temporary confusional states in elderly people. Reports of results with Metrazol in confusional states vary from excellent in 85 per cent of patients to minimal changes. In delirium, perphenazine calms the patient so that he is less upset by hallucinations and delusions, and large doses of hypnotics can be avoided. It is inadvisable to administer a hypnotic with a phenothiazine derivative as the latter potentiates the hypnotic action, frequently giving rise to respiratory difficulties. When a hypnotic becomes necessary, it should be administered slowly and cautiously, giving only enough to permit the patient to sleep.

PAGET'S DISEASE OF THE MALE BREAST.

Sinkler, W. H., and Cooper, T. J. *Am. J. Surg.* **98:** 623 (Oct.) 1959.

This is the eighth case report in the English literature of Paget's disease of the male breast. The only symptom was bleeding from the nipple of six months' duration. The pathologic diagnosis following removal of the breast was Paget's disease associated with carcinoma of the duct. Although no palpable axillary nodes were found, radical mastectomy was performed. The patient has remained well without evidence of recurrence or metastases.

ATRIAL FLUTTER WITH 1:1 A-V CONDUCTION ASSOCIATED WITH PULMONARY EMBOLISM IN THE AGED.

Spivack, A. P.: Sackner, M. A., and Schnabel, T. G. *Am. Heart J.* **59:** 53 (Jan.) 1960.

Atrial flutter with 1:1 atrioventricular conduction is a rare entity. Among 46 cases appearing in the literature, none has occurred in a patient past 60 years of age. Reported here and in the addendum are 3 cases in patients aged 65, 70 and 67 years, respectively. In each the arrhythmia was associated with the occurrence of pulmonary emboli. These cases show that despite advanced age, rapid transmission of atrial impulses across the A-V node may take place. Accepted etiologic factors in atrial flutter with 1:1 A-V conduction include serious myocardial damage; increased sympathetic tone as during exertion, emotional strain, and the induction of anesthesia; the use of quinidine in the treatment of atrial flutter with partial degrees of A-V block which may slow the atrial rate and allow the ventricle to respond to each atrial impulse; and the intravenous administration of atropine to patients with rheumatic heart disease and atrial fibrillation or atrial flutter with 2:1 block. Pulmonary embolism has not previously been reported to cause atrial flutter with 1:1 A-V conduction. The clinical history of one of the patients indicated that pulmonary embolism was the stimulus for the arrhythmia. The finding at necropsy of thrombi in the pulmonary arteries of the second patient and throughout the lungs of the third patient suggested a causal relationship.

TREATMENT OF CARDIAC ARRHYTHMIAS WITH SALTS OF ETHYLENEDIAMINE TETRAACETIC ACID (EDTA).

Surawicz, B.; MacDonald, M. G.; Kaljot, V., and Bettinger, J. C. *Am. Heart J.* **58:** 493 (Oct.) 1959.

An average of 2.8 (0.5 to 4.0) Gm. of Na_2EDTA was given intravenously to 46 patients with cardiac arrhythmias. The side-effects were minor. The concentration of serum calcium decreased on an average of 1.18 mEq./L. Atrial ectopic beats were abolished or significantly suppressed in 7 of 14 patients, and ventricular ectopic beats were suppressed in 16 of 25 patients. In 9 instances of atrial fibrillation and 4 of atrial flutter, Na_2EDTA ws ineffective. Atrial flutter was abolished in 1 patient. Na_2EDTA was about equally effective in suppressing ectopic beats in patients not receiving digitalis as in those receiving it. There was no difference in the effect of Na_2EDTA in patients without heart disease and in those with

varying degrees of heart disease. The success or failure was not related to changes in heart rate or degree of induced hypocalcemia. The suppression of ectopic beats after infusion of Na_2EDTA was attributed to the induced hypocalcemia, because in the majority of patients in whom calcium chloride was given after termination of the infusion of Na_2EDTA, the ectopic beats reappeared. The main effect of induced hypocalcemia on the electrocardiogram consisted of prolongation of the S-T segment and of the coupling interval of the premature beats. The latter was attributed to lengthening of the refractory phase of the ventricular myocardium, which was considered as a possible mechanism of the action of Na_2EDTA on ectopic beats. Intravenous infusion of KCl followed infusion of Na_2EDTA in 10 patients. In addition, 11 patients received an intravenous infusion of 1.3 to 3.0 Gm. of K_2EDTA. The combined administration of chelating agent and potassium appeared to have a stronger antiarrhythmic action than did the infusion of either substance alone in only a very few cases. (Authors' summary.)

ELECTROENCEPHALOGRAPHIC ABNORMALITIES IN PRESENILE ATROPHY.

Swain, J. M. *Neurology* **9:** 722 (Nov.) 1959.

Case reports and electroencephalographic findings are presented for 4 patients with Pick's presenile atrophy and 10 patients with Alzheimer's atrophy in whom the diagnosis was verified histologically in an attempt to distinguish each from the other and to distinguish the group of presenile atrophies from other progressive degenerative disorders of the brain. All cases of Alzheimer's atrophy showed electroencephalographic abnormalities—usually a random, generalized slowing. Paroxysmal dysrhythmia was superimposed in 4 instances, and focal slowing occurred in 5 patients. The characteristic random, disorganized slowing could be distinguished readily from the slowed, but rhythmic and essentially well organized electroencephalogram seen in normal old age groups and in some hypometabolic states. The electroencephalographic changes, however, were not different from those seen in the mentally disorganized, senile psychiatric patient in whom generalized cortical atrophy is also present. The cases of Pick's atrophy showed no focal abnormalities in the electroencephalograms and less evidence of generalized abnormality even when the personality and intellect were profoundly deteriorated. Therefore, the electroencephalogram may miss a diagnosis of Pick's atrophy. A review of patients with presenile atrophy seen in a hospital population has shown that the degree of abnormality manifested in the electroencephalogram usually correlates with the rapidity of progression of the illness at the time, rather than with the specific histologic changes.

ZUR DIAGNOSE DES MAGENKARZINOMS MIT HILFE DER DIPHENYLAMINREAKTION IM MAGENSAFT (THE DIAGNOSIS OF GASTRIC CARCINOMA BY MEANS OF THE DIPHENYLAMINE REACTIONS OF GASTRIC JUICE).

Wada, T.; Ohara, H.; Hosokawa, S., and Morimoto, Y. *Aerztl. Forsch.* **13:** I/231, 1959; through Ciba Literature Review **5:** 3, 1960.

Taking as the starting point the fact that polarographic activity in the gastric secretion declines temporarily following the injection of insulin, the authors looked for new ways of establishing an early diagnosis in cases of gastric carcinoma and developed the diphenylamine (D.P.A.) reaction of the gastric juice as a new colorimetric test. Sixty-four patients with gastric carcinoma, 33 with fresh gastric ulcer, 65 with chronic gastric disorders and, for comparison, 10 normal test subjects, were examined clinically. The D.P.A. reaction proved to be the most sensitive method yet known. Carcinoma was diagnosed correctly in 94 per cent of the cases, and no false positive reactions were obtained. In order to clarify the mechanism of the D.P.A. reaction, tests were carried out to establish the relationship between it and the following: degree of acidity, polarographic activity, concentration of mucoproteins and mucoproteoses, hexose-amine level, and ultraviolet absorption. The authors conclude that a positive D.P.A. reaction is due to dissolution of the superficial mucus which is a consequence or concomitant symptom of the development of gastric carcinoma.

NEWS AND NOTICES

REPORT OF THE SENATE SUBCOMMITTEE ON PROBLEMS OF THE AGED AND AGING

Senator Pat McNamara (D. Mich.), Chairman of the Senate Subcommittee on Problems of the Aged and Aging, has announced the release of the Subcommittee report presenting detailed findings on the needs of America's elderly citizens, with recommendations for legislative action. Dissenting views of the Subcommittee minority are included in the report.

The Subcommittee findings are based on data compiled from evidence gathered by the Subcommittee at hearings held in Washington and in seven cities across the nation, personal visits to representative facilities for the aged, an intensive survey conducted by the Subcommittee, and extensive staff studies and analyses of programs and problems.

The first chapter of the report, entitled "The Emergence of a National Problem," deals with the changing pattern of the American economy and family structure, and relates these changes to the current problems. The interrelatedness of the complex problems of aging is dramatically revealed in case histories which illustrate the chain reaction effect of such problems on other members of the family and the economy in general. "The so-called 'problems of the aged' are not theirs alone, but are properly the concern of all society," the report notes.

Subsequent chapters deal with the employment problems of older Americans, income needs, health status, financing of medical care, housing conditions, nursing homes, social services for independent living, and the educational needs of the aged and aging.

Calling for a clear-cut policy to meet the needs of America's senior citizens, the report emphasizes: "Old attitudes and old policies no longer apply or suffice. Indeed, if they persist, they may prove injurious to our whole society."

The twelve recommendations for legislative action were endorsed by the Subcommittee majority: Chairman Pat McNamara, Senators Jennings Randolph (W. Va.), Joseph S. Clark (Pa.), and John F. Kennedy (Mass.). The Republican members are Senators Everett M. Dirksen (Ill.) and Barry Goldwater (Ariz.).

A limited number of copies of the report are available in Room 249, Senate Office Building.

PROGRAM

SEVENTEENTH ANNUAL MEETING

OF THE

AMERICAN GERIATRICS SOCIETY

Thursday, June 9 and Friday, June 10, 1960

The Americana Hotel, Bal Harbour, Miami Beach, Florida

THURSDAY, JUNE 9, 1960

MORNING SESSION—Medallion Room

8:00 REGISTRATION

9:00 Presiding Officer: *Frank Glenn, M.D.*

TEMPORAL LOBE ABNORMALITIES IN THE SENESCENT ELECTROENCEPHALOGRAM

Ewald W. Busse, M.D., Professor of Psychiatry; Chairman, Department of Psychiatry, Duke University, Durham, N. C. and *Walter D. Obrist, Ph.D.*, Associate Professor of Medical Psychology, Duke University, Durham, N. C.

ALTERATIONS IN NEUROLOGICAL STATUS WITH AGE and THE PHYSICAL PROBLEMS OF PSYCHIATRICALLY HOSPITALIZED ELDER PEOPLE

Ernest G. Newman, M.D.; *Robert H. Dovenmuehle, M.D.*; *Ewald W. Busse, M.D.*, Department of Psychiatry and Center for the Study of Aging, Duke University Medical Center, Durham, N. C.

10:30 INTERMISSION

11:00 Presiding Officer: *Hollis E. Clow, M.D.*

NEUROHUMORAL FACTORS IN LIPID MOBILIZATION

Robert F. Klein, M.D.; Sanuel J. Friedberg, M.D.; E. Harvey Estes, Jr., M.D.; Morton D. Bogdonoff, M.D., Duke University Medical Center and Veterans Administration Hospital, Durham, N. C.

TRANQUILIZERS AND THE AMBULATORY GERIATRIC PATIENT

Frank J. Ayd, Jr., M.D., Chief of Psychiatry, Franklin Square Hospital, Baltimore, Md.

PSYCHOLOGICAL STUDIES IN GERIATRIC HEMIPLEGIA

Edward J. Lorenze, M.D., Medical Director, Burke Foundation, White Plains, N. Y.; Assistant Professor of Clinical Medicine, Cornell University Medical College, N. Y.

12:30 LUNCHEON

AFTERNOON SESSION—Medallion Room

2:00 Presiding Officer: *Edward Henderson, M.D.*

THE DUAL NATURE OF AGING

Edward L. Bortz, M.D. Chief, Medical Service, Lankenau Hospital, Philadelphia, Pa.

KEEP THE AGED HEALTHY (PREVENTION OF CERTAIN CHRONIC ILLNESSES IN THE AGED)

Charles L. Wilbar, Jr., M.D. Secretary of Health, Commonwealth of Pennsylvania, Harrisburg, Pa.; Visiting Professor of Public Health and Preventive Medicine, University of Pennsylvania Medical School, Philadelphia, Pa.; Lecturer, Graduate School of Public Health, University of Pittsburgh

PLANNING CARE FOR THE GERIATRIC PATIENT

Ruth Freeman, Ed.D., Staff Member, Rockefeller Foundation, New York, N. Y.; Associate Professor, Public Health Administration, Johns Hopkins School of Hygiene and Public Health, Baltimore, Md.

PLANNING FOR AGING

Joseph H. Bunzel, J. D., Associate Professor of Social Research, Richmond Professional Institute, College of William and Mary, Richmond, Va.

POPULATION AGING—WHERE IT'S TAKING US

Clark Tibbitts, Chief, Program Planning, Special Staff on Aging, U. S. Department of Health, Education and Welfare, Washington, D. C.

4:45 BUSINESS MEETING

6:30 ANNUAL RECEPTION AND DINNER (Dancing will follow)
Westward Room (Mezzanine)
Presentation of Willard O. Thompson Award

FRIDAY JUNE 10, 1960

MORNING SESSION—Medallion Room

8:00 REGISTRATION

9:00 Presiding Officer: *Thomas H. McGavack, M.D.*

GERIATRICS, GERONTOLOGY AND GASTROENTEROLOGY—A CHALLENGE TO THE CLINICIAN

Karver L. Puestow, M.D., Professor of Medicine, University of Wisconsin Medical School, Madison, Wis.

NUTRITIONAL PROBLEMS AND OPERABILITY IN THE AGED

William H. Harridge, M. D., Clinical Assistant Professor of Surgery, University of Illinois College of Medicine, Chicago, Ill.; Associate Attending Surgeon, St. Francis Hospital, Evanston, Ill. and *Warren H. Cole, M. D.*, Professor and Head, Department of Surgery, University of Illinois College of Medicine, Chicago, Ill.

RESUSCITATION FROM SUDDEN DEATH OCCURRING OUTSIDE THE OPERATING ROOM SUITE

George R. Holswade, M. D., Associate Professor of Clinical Surgery, Cornell University Medical College, New York, N. Y.; Associate Attending Surgeon, The New York Hospital, New York, N. Y.

10:30 INTERMISSION

10:45 Presiding Officer: *Edward B. Allen, M. D.*

SYME AMPUTATION IN THE AGED

Robert L. Bradley, M. D., Chief, Surgical Service, Veterans Administration Hospital, Huntington, W. Va.

MANAGEMENT OF OCCLUSIVE ARTERIAL DISEASE OF THE LOWER EXTREMITIES IN ELDERLY PATIENTS and

SURGICAL CONSIDERATIONS OF PERIPHERAL ARTERIOSCLEROTIC ANEURYSMS

Michael E. DeBakey, M. D., Professor of Surgery, Baylor University College of Medicine; Surgeon in Chief, Jefferson Davis Hospital; Senior Attending Surgeon, Methodist Hospital; Chief Surgical Consultant, Veterans Administration Hospital, Houston, Texas

Denton A. Cooley, M. D., Associate Professor of Surgery, Baylor University College of Medicine; Attending Surgeon, Jefferson Davis and Methodist Hospitals; Consultant, Veterans Administration Hospital; Chief, Cardiovascular Service, Texas Children's Hospital, Houston, Texas

E. Stanley Crawford, M. D., Associate Professor of Surgery, Baylor University College of Medicine; Attending Surgeon, Jefferson Davis and Methodist Hospitals; Consultant, Veterans Administration and Texas Children's Hospitals, Houston, Texas

George C. Morris, Jr., M. D., Assistant Professor of Surgery, Baylor University College of Medicine; Attending Surgeon, Jefferson Davis and Methodist Hospitals; Consultant, Veterans Administration and Texas Children's Hospitals, Houston, Texas

William H. Edwards, M. D., Fellow in Cardiovascular Surgery, Baylor University College of Medicine, Houston, Texas

CANCER CHEMOTHERAPY BY REGIONAL PERFUSION

Oscar Creech, Jr., M. D., Professor and Head, Department of Surgery, Tulane University School of Medicine, New Orleans, La.

12:45 LUNCHEON

AFTERNOON SESSION—Medallion Room

2:00–4:30 Presiding Officer: *Edward L. Bortz, M. D.*

THE TREATMENT OF CORONARY DISEASE IN OLDER PEOPLE

Arthur M. Master, M. D., Consultant Cardiologist, The Mount Sinai Hospital, New York, N. Y.; Consultant Cardiologist, The Englewood Hospital, Englewood, N. J.; Consultant in Cardiovascular Disease, U. S. Marine Hospital, Staten Island, N. Y.

CLINICAL MANAGEMENT OF HYPERTENSION IN THE OLDER PATIENT

Morton M. Halpern, M. D., Clinical Associate Professor of Medicine, University of Miami Medical School; Chief of the Hypertension Clinic, Miami, Florida

USE OF MODERN DIURETICS IN THE AGED

George E. Burch, M. D., Chairman and Head, Department of Medicine, Tulane University, New Orleans, La.

PROGRESS REPORT ON LONG-TERM USE OF DIETS HIGH IN POLYUNSATURATED FATS IN DIABETIC AND NONDIABETIC PATIENTS

Laurance W. Kinsell, M. D., Director, Institute for Metabolic Research, Highland-Alameda County Hospital, Oakland, Calif.

URINARY ESTROGEN AND GONADOTROPHIN EXCRETION AND PLASMA CORTICOID RESPONSE TO ACTH IN ELDERLY WOMEN

Robert L. Nielsen, M. D., Mason Clinic, Seattle, Wash.

OFFICERS SESSIONS WEDNESDAY, JUNE 8, 1960

4:00 P.M.	Committee Meetings	Pan-American Room
6:00 P.M.	Dinner	Gaucho Room
8:00 P.M.	Advisory Council Meeting	Pan-American Room
9:00 P.M.	Board of Directors Meeting	Hawaiian Room
	Conference and Press Hospitality Suite	Caribe Room